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Spine Stereotactic Body Radiation Therapy (SBRT): Using biological objectives in treatment planning a comparative plan study

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Abstract

Introduction

The purpose of the study is intended to determine if gEUD optimization can be useful in the treatment planning for SBRT to the spine. The main goal was to study the dose effects when placing gEUD objectives on the targeted vertebral structure (Target gEUD) and spinal cord (Upper gEUD). Furthermore, to provide a better understanding of the utility of this tool.

Methods

Two planning techniques for SBRT spine treatments were compared retrospectively on 10 radiation therapy patients. The Varian Eclipse treatment planning system was utilized with the volumetric modulated arc therapy treatment technique. The planning techniques used different objectives in the optimizer. One plan used dose volume (DV) objectives on both the Spinal cord and target. The other plan used a combination of DV and generalized uniform equivalent objectives (gEUD) on both spinal cord and target. Plans were evaluated using dose volume histograms and statistical analysis of each plan.

Results

Based on the comparative analysis between the two planning techniques it was found that the specific use of the target gEUD in this setting did not improve the plan quality. The target gEUD constraint in the optimizer while providing a homogenous dose to the target increased the maximum dose beyond what would be clinically acceptable. Both plans were able to spare the spinal cord effectively.

Conclusion

For the treatment of the spine in the SBRT setting the sparing of the cord is of utmost importance and both planning techniques managed this well. The use of the target gEUD in the SBRT setting did not provide a benefit when looking at the overall plan quality. Recommendations to the use of the target gEUD should be further investigated.

Introduction & Background

The spine is a common location of distant metastatic spread within the body. According to the American Cancer Society, about 400,000 new cases of bone metastasis are diagnosed in the United States each year[1]. Bone metastasis can cause pain, pathologic fracture, or spinal cord compression if left untreated[1]. Although spinal metastases are not curable, they can be controlled in many cases.

Radiation therapy (RT) has been a mainstay in treating spinal metastasis with the primary goal of pain relief. Conventional external beam radiotherapy (cEBRT) is often the standard treatment technique.

Previous studies have shown that a low-dose treatment delivered in a short course can be as effective as a higher dose over an extended course of treatment in managing pain[2]. Even though these regimens of treatment can be beneficial and have a place in many palliative cases, Study RTOG 9714 found that both series of treatment only had a 51% pain response rate at three months[2]. One of the limiting factors in treating cEBRT is the low tolerance doses of close Organs at Risk (OARs). Prioritizing sparing OARs to prevent further patient complications leads to covering the metastatic site with a lower effective treatment dose[3].

Emerging technology has benefited those with cancer in the early detection of metastatic lesions. Detection of bone lesions can be challenging but advances in imaging have made it possible to identify localized metastatic spread[4]. The most common imaging used to diagnose bone metastasis are skeletal scintigraphy (SS), Radiography, Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) [4]. PET imaging has emerged as

an important clinical application in the oncology setting. The ability of PET imaging to scan the entire body in a short amount of time coupled with its substantially higher resolution compared to other imaging modalities has made it a mainstay in the clinical management for cancer patients[4]. MRI is another imaging modality that has become a mainstay in the early detection of metastatic disease. Similar to PET, whole-body MRI development has made it possible to detect metastatic spread in a short time period[4]. As imaging and detection has developed to benefit the cancer patient population the treatment options have advanced similarly.

With imaging providing the oncology community the ability for earlier detection of metastatic spread, changes in how we categorize these patients has evolved as well. An intermediate stage of metastatic disease may be present and thus how it is treated should be investigated[5]. This intermediate stage of metastatic cancer was initially coined in the mid-1990s by Hellman and Weichselbaum. Cancer spread initially was theorized to be orderly in nature[5]. Starting at the primary tumor site then spreading to the lymph nodes and finally to distant sites within the body[5]. Further research suggested that clinically evident disease is already in a systemic state and that involvement outside the primary tumor site is a sign of distant disease[5]. While both theories may have some validity Hellman and Weichselbaum suggested that this may be too confining with what we now know about cancer progression[5]. Their theory married the two ideas with the thought that there is a biologic spectrum between localized and distant spread with many intermediate clinical states of the cancer[5]. These intermediate states of metastasis may be limited to a few distant organs during the course of tumor progression. Hellman and Weichselbaum coined this stage of disease, oligometastases.

Early detection of this oligometastatic state of the cancer has opened the door to managing this diagnosis quite differently compared to distant metastatic spread treatment options. Some patients with more favorable disease and prognosis may benefit from a more targeted treatment specific to the single metastatic site[6].

The vast improvements in radiotherapy treatment techniques have provided the ability to treat patients with ablative intent using higher doses, defined as Stereotactic Body Radiation Therapy (SBRT). SBRT treatment needs to be approached with extreme caution with respect to OARs near the treatment site. Specific constraints need to be met to prevent serious injury to the patient. Regarding metastatic spinal SBRT treatments, the spinal cord is the most critical organ at risk. The spinal cord is considered a serial structure; any damage to a partial volume of the structure can cause significant neurological impairment, with the endpoint being radiation myelopathy[7]. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) suggests dose (Gy), or dose per volume parameters for conventional fractionation and stereotactic radiation to critical structures[8]. For the spinal cord, to avoid Myelopathy or other effects, the maximum dose allowed for SBRT is less than 13 Gy for a single fraction and 20 Gy for three fractions with partial cord cross-section irradiated[8].

With Volumetric Modulated arc Therapy (VMAT) in the SBRT setting, a very conformal dose can be achieved while sparing nearby OARs. The Treatment planning system (TPS) utilizes inverse optimization processes controlled manually by the use of objectives that give the program a roadmap to deliver the desired dose to the treatment volume while sparing OARs. Due to the interactive approach to optimizing a treatment plan, many factors need to be considered to provide maximum OAR sparing and planning target volume (PTV) coverage[9].

The optimization tool in the TPS allows the user to define specific objectives based on physical dose or dose-volume (DV) constraints[10]. The use of DV constraints is somewhat limiting and may not represent the actual biological responsiveness of the tissue[10]. One of the newer photon optimization (PO) tools that have been added to recent versions of the Eclipse TPS is a biological based objective called generalized equivalent uniform dose (gEUD) [11]. The gEUD function is an extension of the equivalent uniform dose (EUD) that represents the biologically equivalent dose, which, if given uniformly, leads to the same cell kill in the tumor volume as the actual non-uniform IMRT dose distribution[11]. When optimizing, gEUD can be used for both OARs and target volumes, while EUD was solely for target volumes[11].

Three gEUD biological objectives can be utilized in the Eclipse optimizer, Upper gEUD, lower gEUD, and Target gEUD[10]. Fogliata et al., explains that gEUD can be used "as a single organ specific parameter to account for the biological response according to the delivered dose distribution in that organ." The optimizer's gEUD objectives are driven by the function alpha (α). Fogliata et al.[10] explains, "The parameter α can vary from +0.1 to +40 for upper gEUD, from -40 to +1, excluding 0, for Lower gEUD and Target gEUD." A high α value is used to drive down the maximum dose and used on serial structures[11]. A value close to 1.0 is used to manage the mean dose to a parallel structure[11].

In recent years, studies have shown that using gEUD with specific α values can help spare OARs without compromising target coverage. Fogliata et al., looked at how certain α values from +0.1 - +40 within the TPS affect OARs sparing and target coverage. They concluded gEUD optimization to be a useful tool[11]. The use of the target gEUD tool within

the optimizer has not had as much research published and this will be taken into consideration when planning but investigation into this optimization tool will be part of the overall research at hand.

This study intends to determine if gEUD optimization can be useful in the treatment planning for SBRT to the spine. The main goal is to study the dose effects when placing gEUD objectives on the targeted vertebral structure (Target gEUD) and spinal cord (Upper gEUD). Furthermore, provide a better understanding of the utility of this tool.

Research Question

Will the use of gEUD in the TPS optimizer improve the sparing of the spinal cord and provide conformal coverage and lower maximum dose to the targeted spine?

Methods and Materials

Patient Selection

This is a retrospective study of 10 patients previously treated for metastatic disease of the thoracic or lumbar spine using SBRT technique with 27 Gy being delivered over the course of three fractions. The patients were de-identified in the Varian Eclipse TPS by an independent party not associated with the research. The researcher then replanned the de-identified patients using the same beam configurations, same prescription, and the same treatment volumes as defined by the same physician.

IRB

The researcher completed the needed CITI courses through Grand Valley State University (GVSU) and Roswell Park Comprehensive Cancer Center (RPCCC). Once these were completed a research proposal was submitted to the radiation oncology administration and the Internal Review Board (IRB). The proposal outlined how the researcher would handle Protected Health Information (PHI) and manage the process of de-identifying patient data in compliance with hospital research standards. The research project was then approved by the hospital IRB committee and GVSU's IRB board.

Simulation

Each patient was consulted for treatment by the Radiation Oncology team. After consent was given, the patients were simulated in treatment position using the same GE Lightspeed CT simulator. Patients were positioned headfirst supine in a BodyFIX stereotactic immobilization device for exact reproducibility of daily setup by the therapy team[12]. The patient's arms were placed above their head in a comfortable position. A scout image was performed to set the isocenter on the specific vertebral body for treatment by the attending physician. The patients were marked with a three-point setup for correct daily positioning. The Immobilization device was also marked at isocenter to aid in patient setup each day.

Planning

Following the simulation of the patient, the images were imported into the Varian Eclipse Treatment Planning System (TPS) version 15.1. All plans used Acuros XB version 15.6.05 (Varian Medical Systems) calculation algorithm and treated on the Varian TrueBeam with High Definition 120 Leaf Multileaf Collimator (HDMLC). The same radiation oncologist completed all contouring of target volumes and Organs at Risk (OARs) in the TPS. Any OAR

within 3.0 cm circumferentially of a target was contoured. For a target in the cervical/thoracic spine this list would include, Lungs (Left/Right/combined), Heart, Great Vessels, Trachea, Esophagus, Chest wall, Brachial plexus, Skin, Liver, Bile Duct, Kidney (left/Right), Larynx, Stomach, and Rib. For a target in the lumbar spine this list would include, Heart, Stomach, Duodenum, Kidney (Left/Right), Bowel, Rectum, Bladder, Skin, Lungs (Left/Right/combined), Liver, Bile Duct, Chest Wall, and femurs. For the purpose of this study the OAR region of interest was 3.0 cm superior and inferior to the Spinal Cord, Cauda Equina (if applicable), and Sacral Plexus (if applicable) but all OAR constraints were taken into consideration. The contoured target structures included the Gross Tumor Volume (GTV) and Planning Tumor Volume (PTV) which was a 5.0 mm expansion of the GTV. Structures were also created for utilization during planning. These included a PTV minus the spinal cord with a 1.0 mm margin (PTV_{opti}), and PTV plus 2.0 cm margin in any direction PTV_{+2cm}).

After all contouring and relevant structures were delineated the planning process began. All of the initial plans were completed by the same Dosimetrist using Stereotactic Body Radiotherapy (SRS) technique and approved by the radiation oncologist. The plan consisted of 10 MV Flattening Filter Free (FFF) beams with 4 partial arcs (270°-181°, 181°-270°, 90°-179°, and 179°-90°) with a counter clockwise, clockwise, clockwise, counter clockwise beam path and collimator angles of 30°, 90°, 30°, 90° respectively. The MLCs were initially fit to the target volume with a 0.1 mm margin and jaw tracking was disabled. Beam configurations were consistent for all study cases. The Target volumes were all treated to 27 Gy in three fractions. Planning objectives are as follows, respect the spinal cord, cauda Equina, sacral plexus dose constraints: Spinal cord V0.03cc<22.5Gy, V1.2cc<13Gy. Cauda Equina V0.03cc<25.5Gy,

V5cc<21.9Gy. Sacral Plexus V0.03cc<24Gy, V5cc<22.5Gy. Target coverage: 95% of the PTV covered by the prescription dose. Hotspots within the target were acceptable, dose > 105% restricted to the PTV. The ratio of the prescription isodose volume to PTV volume < 1.2 which determines the conformity index. Target coverage and dose compactness while sparing the spinal cord was prioritized over OAR constraints.

The initial planning (DV plan) approach for each patient looked at dose-volume objectives (DVOs) in the optimizer to meet treatment goals. A second plan was created for each patient by copying the initial plan and adding gEUD constraints to the PTV and Spinal cord (gEUD plan). The DV plan had a lower and upper objective on the PTV_{opti} and PTV, a lower objective on the GTV, two upper objectives on the Spinal Cord/Cauda Equina. The PTV_{opti} lower objective was set at 97% of the volume to receive 100% of the prescribed dose and the PTV upper objective was set at 0% of the volume to receive 125% of the prescribed dose. The lower objectives on the GTV were set at 50% of the volume to receive 115% of the prescribed dose. The Spinal Cord/Cauda Equina upper objectives were set at 0% of the structure to receive 50% of the prescribed dose and 2% of the structure to receive 37% of the prescribed dose. Mean Objectives were added to all OARs. To ensure rapid dose fall off the Normal Tissue Objectives (NTOs) tool was utilized with the start dose of 100% having a fall off of 0.6 to 45% of the prescribed dose and a distance from the target border of 0 cm. After the first optimization, the plans were evaluated, and further optimization was done to meet treatment constraints. The planner used a scale of 0-300 for the priorities, Spinal Cord/Cauda Equina were kept at 250, Target volumes 150, and OARs 75. During optimization, adjustments were made, to ensure coverage and Spinal Cord/Cauda Equina constraints were met. All plans

were normalized so that 100% of the dose covers 95.1% of the target volume to meet constraints and maintain hotspots within the GTV if possible. Plans were run through the optimizer multiple times until proper conformity of the PTV was best achieved, and proper dose fall-off was maximized.

The gEUD plan utilizing gEUD constraints were then created by copying the DV plan and adding gEUD constraints to the PTV and spinal cord. Target gEUDs were added to the PTV with an alpha value of -10 with the intent of achieving conformal target coverage. Priority was initially set at 150. Two Spinal Cord/Cauda Equina Upper gEUD objectives were added with an alpha values of 38 and 1 and priorities of 200. Optimization restarted, and target coverage was initially observed on the dose-volume histogram. The dose value for the spinal cord were initially set at the actual calculated dose and adjusted in minor increments as low as reasonably possible without target coverage being effected but meeting plan objectives.

Data collection and evaluation for all the plans were completed when target coverage and spinal cord constraints met. Statistical data collected: minimum dose, maximum dose, conformity index (CI) and Gradient Index (GI) to the PTV; Along with the maximum, mean, D0.03cc and D1.0cc to the spinal cord.

Results

The intent of this study was to see if gEUD objectives used in the optimizer could produce a better plan compared to a DV objective based plan. The goal was to see if the gEUD objectives could result in improved dosimetric effects with respect to PTV and spinal cord

structures and provide a more thorough understanding of the gEUD optimizer tool. Sign Test statistics were used to compare the dosimetric differences between the two plans.

Conformality Index

The conformity index (CI) for the target PTV were evaluated for both plans as seen in Table 1. A Sign Test statistic indicated that the DV plans CI were statistically significant compared to the gEUD plan $p = 0.002$ (Figure 4). The mean CI score for the DV plans were 1.004 compared to 1.184 for the gEUD plans. The median CI score for the DV plans were 0.97 with a range of 0.25, compared to the median CI score for the gEUD plans of 1.125 with a range of 0.58.

Gradient Index

The Gradient Index (GI) for the target PTV were evaluated for both plans as seen in Table 1. A Sign Test statistic indicated that the DV plans GI were statistically significant compared to the gEUD plan $p = 0.021$ (Figure 5). The mean GI score for the DV plans were 1.136 compared to 1.194 for the gEUD plans. The median GI score for the DV plans were 1.025 with a range of 0.89, compared to the median GI score for the gEUD plans of 1.145 with a range of 0.88.

PTV

The minimum dose and maximum dose to the PTV were evaluated for both plans as seen in Table 1. The maximum and minimum PTV doses did not show a significant difference, $p = 0.754$ and $p = 0.109$ respectively (Figures 2&3).

Spinal Cord

The maximum, mean, D0.03cc and D1.0cc to the spinal cord were evaluated for both plans. The maximum and mean spinal cord doses did not show a significant difference, $p = 0.109$ and $p = 0.754$ respectively (Figures 6&7). The D0.03cc and D1.0cc spinal cord doses did not show a significant difference, $p = 0.754$ and $p = 1.000$ respectively (Figures 8&9).

Discussion

The purpose of this study is to analyze two different treatment planning techniques for spinal metastasis using SBRT. The first plan focused on the standard DV objectives in the optimizer. The second plan focused on the use of gEUD objectives in the optimizer aiming at improving target coverage and spinal cord avoidance with a sharp dose gradient between the two structures. The dosimetric effects for the target PTV and Spinal cord were evaluated for each plan. The goal of this study was to improve plan quality with the use of gEUD objectives.

Conformality Index

The conformity index is the cornerstone of SBRT treatments. The ratio of the prescription isodose volume to PTV volume < 1.2 is what represents the rapid dose fall-off gradient outside of the target needed in the SBRT setting. The goal of using a target gEUD (high alpha and priority settings) on the PTV was intended to provide a more conformal dose to the PTV. This was not evident for the gEUD plans and conversely resulted in considerable effects to the overall plan quality. The results were a bulging effect around the PTV due to the optimizer working at achieving the requested conformal dose, see figure 10. The result was

losing the conformity for the gEUD plans which resulted in higher CI values. The researcher could have considered relaxing the target gEUD objective which potentially could have resulted in a more rapid dose fall-off and lower CI score. The overall understanding of how the target gEUD is best utilized could be explored.

Gradient Index

Based on the SBRT protocol followed for the treatment planning of these cases there is no minimum gradient index that needs to be achieved. The gradient index is another representation of a sharp dose fall-off from PTV to normal tissue. Similar to the results seen with the CI, the GI were significantly altered in the gEUD plan due to the use of the target gEUD. The use of the target gEUD with high alpha and priority objectives in the optimizer prevented the sharp fall off preferred at the PTV edge in the SBRT setting, see Figure 11.

Planning Considerations

A clinically acceptable plan using gEUD objectives could have potentially been achieved if some changes were made during the planning process. If the priority on the target gEUD was reduced this could have potentially allowed for the optimizer to focus on other objectives thus providing a more acceptable CI and GI index which were found to be significantly better for the DV plans. The Target gEUD objective showed that it is a powerful tool when optimizing a treatment plan. Another potential adjustment would be to utilize the Target gEUD objective on the GTV as opposed to the PTV. This would allow the high dose to be targeted at the GTV and at the same time allow the other objectives set in the optimizer to focus on delivering a clinically acceptable conformal dose with rapid fall-off.

Managing dose to the spinal cord is of utmost importance when it comes to treating adjacent vertebral bodies. Both plans meet dose constraints to the spinal cord with respect to cord max dose. The DV plan utilized a max dose constraint as well as a mean dose constraint. The gEUD plan utilized two upper gEUD constraints one pushing on the tail (point dose) of the DVH curve and another on the entire (mean) of the DVH curve. The spinal cord constraints were set at a higher priority and would always win out over PTV coverage even if the structures were overlapping. Both the DV and gEUD plans managed the spinal cord goals with no significant benefit one way or the other.

Limitations and Future Research

To study the practical use of biological objectives in the SBRT setting, the researcher chose to only look at spinal metastasis cases. To answer the question as to whether one planning technique proved to be better than the other, some limitations in the research need to be considered. First, the experience in DV based planning far exceeds that of gEUD planning. The trial and error utilizing gEUD objectives added to the planning time should be taken into consideration. As well as, the amount of available research using DV objectives in the planning system is vast compared to gEUD objective based planning. The researcher had no experience with using gEUD objectives in the planning software and took some to learn what works best with regards to the alpha values and priorities. The researcher suspects that when planning, the use of the target gEUD with a high alpha value and high priority was pushed too hard and caused the loss of the sharp dose gradient needed in the SBRT setting. Although the goal of a high alpha value is the push on the tail of the DVH curve, the research suggests otherwise. Consequently, the high priority set on the target gEUD may have put too much of a cost function on this objective which took away other objectives that would have managed the dose

gradient needed for SBRT spine planning. More research on the use of alpha values and priorities when using the Target gEUD function is needed.

Another limitation to the study is that DV objectives were utilized in both the DV plans and gEUD plans. To truly compare DV objective based planning to gEUD objective based planning further research would be needed. The use of the NTO function in the optimizer could be a limitation to the study as well. The NTO was manually set for both the DV plans and gEUD plans with the goal of aiding in the sharp dose gradient at the vertebral body/spinal cord interface. This was achieved for both plans. Further research to see if the gEUD objectives would do a good job at carving out the dose around the spinal cord could be helpful in understanding the functional ability of biologically based objectives.

Conclusion

The research presented shows that there are benefits and drawbacks to the use of gEUD objectives in the optimization of spinal SBRT cases. Experience with the use of biologically based planning objectives played a major role in understanding the overall influence they can have on a treatment plan. This may be a contributing factor to the gEUD plans falling short of what would be clinically acceptable.

PTV coverage and Spinal cord sparing can best be achieved with DV based plans and are more clinically applicable compared to how the biological objectives were utilized in this research. Conformality and dose gradient were better managed with the use NTO and DV based objectives. Spinal cord avoidance can be managed with upper gEUD objectives. More research is needed when utilizing the target gEUD tool in the optimizer. Potential adjustments to the use

of gEUD objectives could prove that it can be a useful tool in the SBRT setting. Target gEUD objectives are a very powerful tool and caution should be taken when they are used in the planning process. Further investigation into the use of DV and Upper/lower gEUD objectives for spine SBRT cases may prove to be practical and clinically useful.

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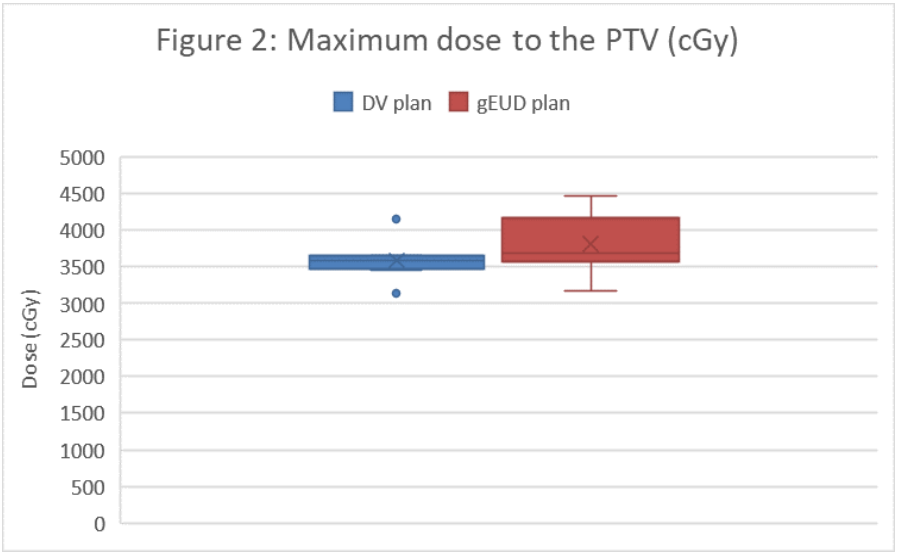
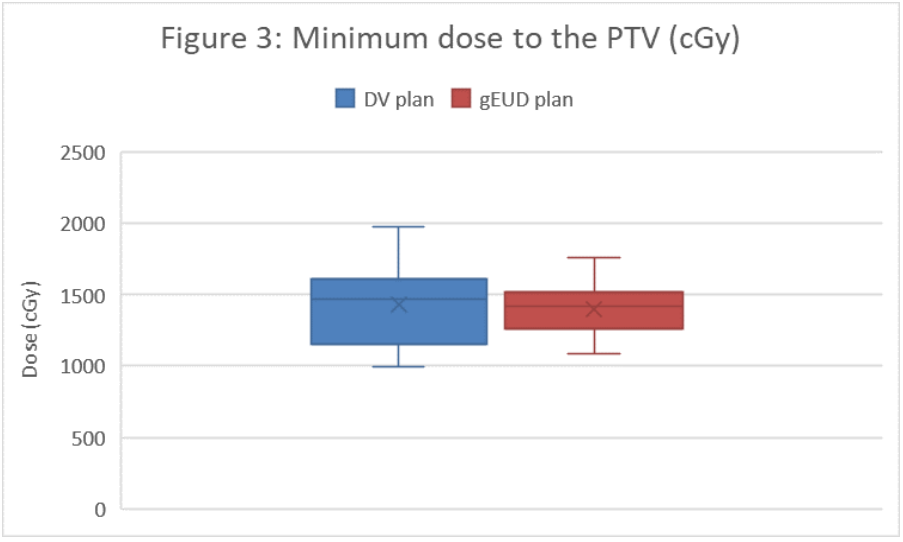
Figure 1. Test Statistics[a]

	Conformity Index gEUD Plan - DV Plan	Gradient Index gEUD Plan - DV Plan	Max Dose gEUD Plan - DV Plan (Gy)	PTV_Min gEUD Plan - DV Plan (Gy)	Dmax Cord gEUD Plan - DV Plan (Gy)	Dmean Cord gEUD Plan - DV Plan (Gy)	D0.03cc Cord gEUD Plan - DV Plan (Gy)	D1.0cc Cord gEUD Plan - DV Plan (Gy)
Exact Sig. (2-tailed)	.002[b]	.021[b]	.109[b]	.754[b]	.109[b]	.754[b]	.754[b]	1.000[b]

a. Sign Test
b. Binomial distribution used.





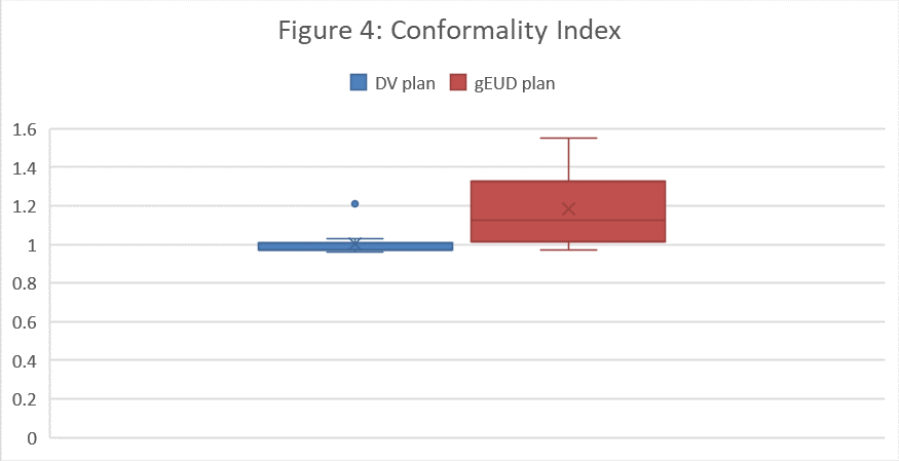


Figure 4: Conformality Index
DV plan
gEUD plan
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0

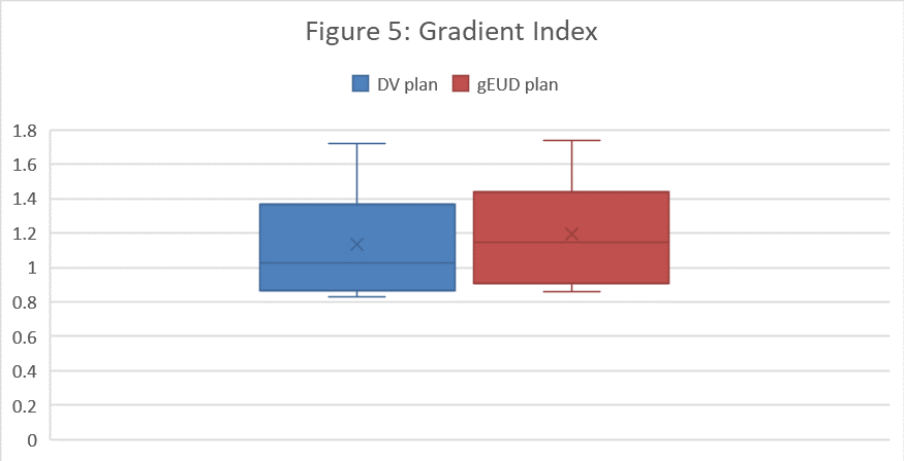


Figure 5: Gradient Index
DV plan
gEUD plan
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0

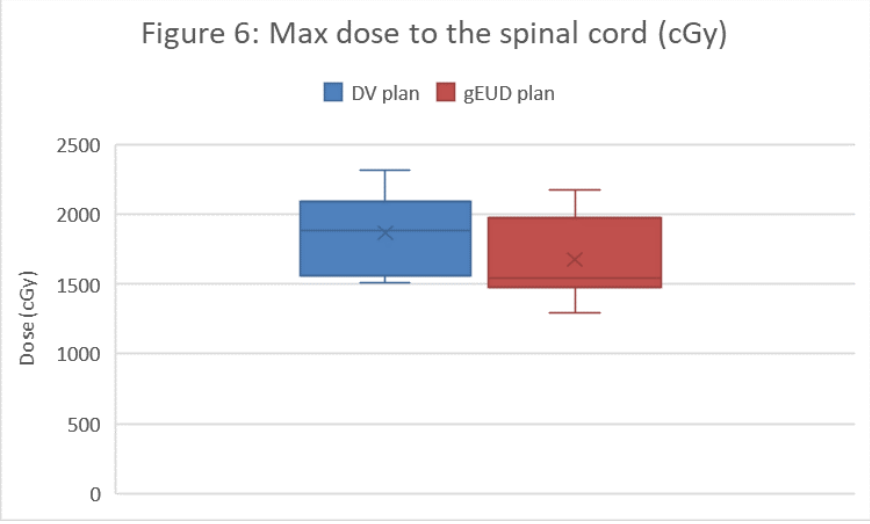


Figure 6: Max dose to the spinal cord (cGy)
DV plan
gEUD plan
Dose (cGy)
2500
2000
1500
1000
500
0

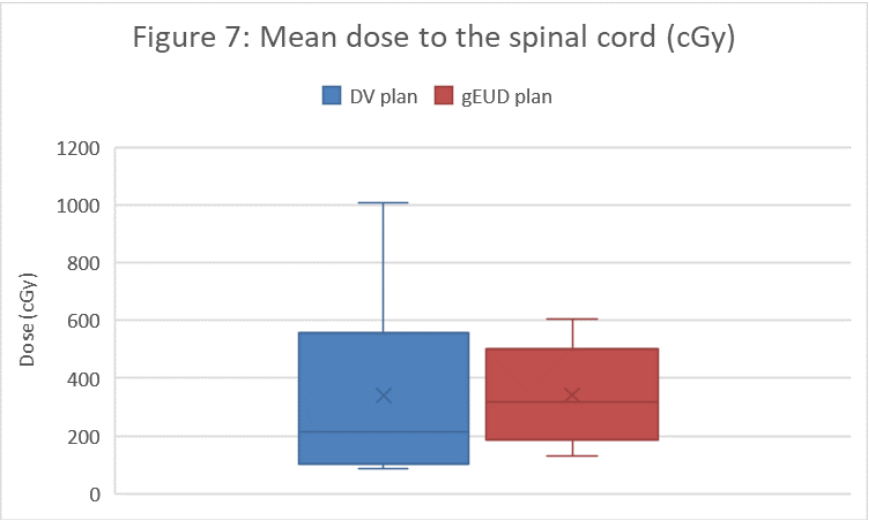


Figure 7: Mean dose to the spinal cord (cGy)
DV plan
gEUD plan
Dose (cGy)
1200
1000
800
600
400
200
0

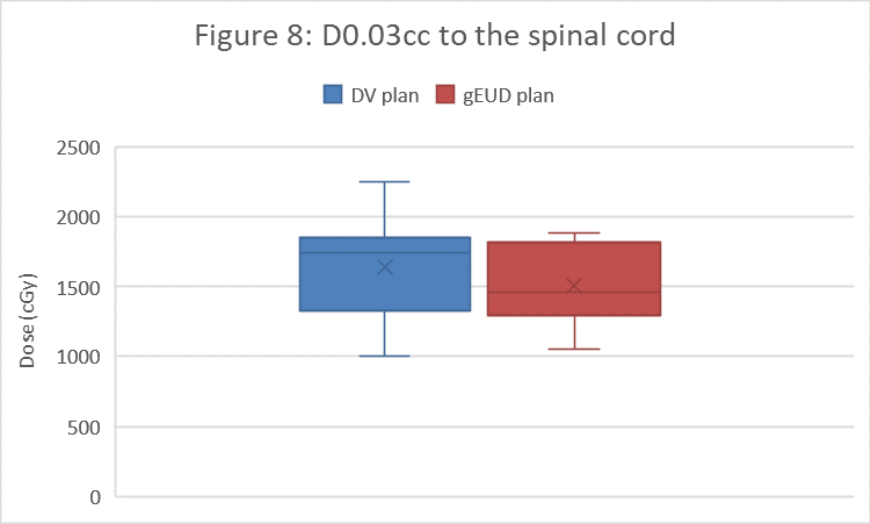


Figure 8: D0.03cc to the spinal cord
DV plan
gEUD plan
Dose (cGy)
2500
2000
1500
1000
500
0

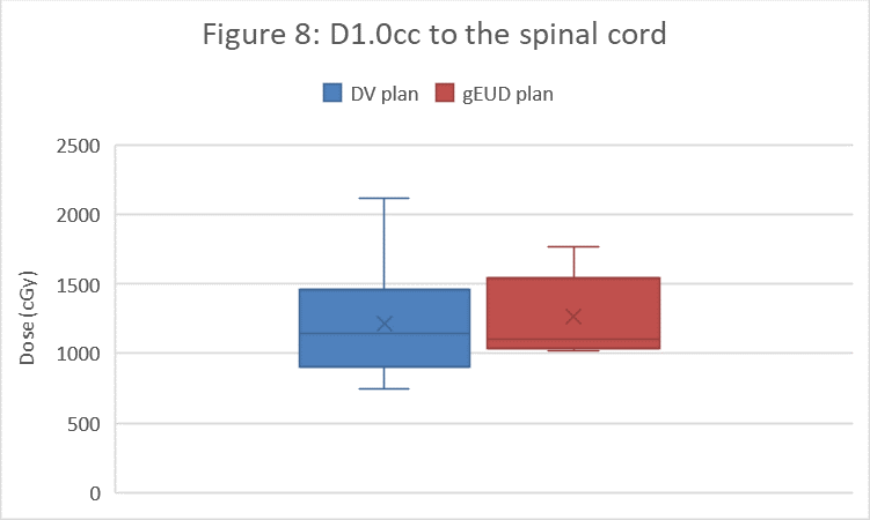


Figure 8: D1.0cc to the spinal cord
DV plan
gEUD plan
Dose (cGy)
2500
2000
1500
1000
500
0

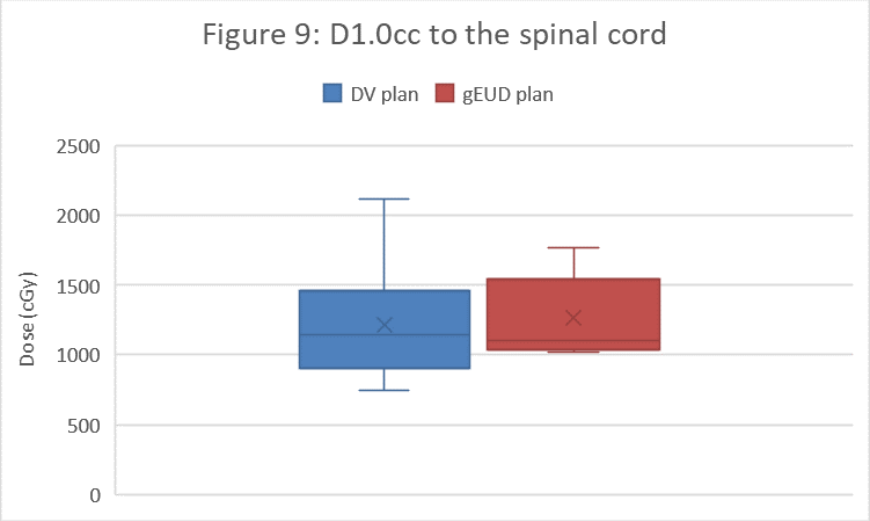


Figure 10: DV plan (left) and gEUD plan (Right)

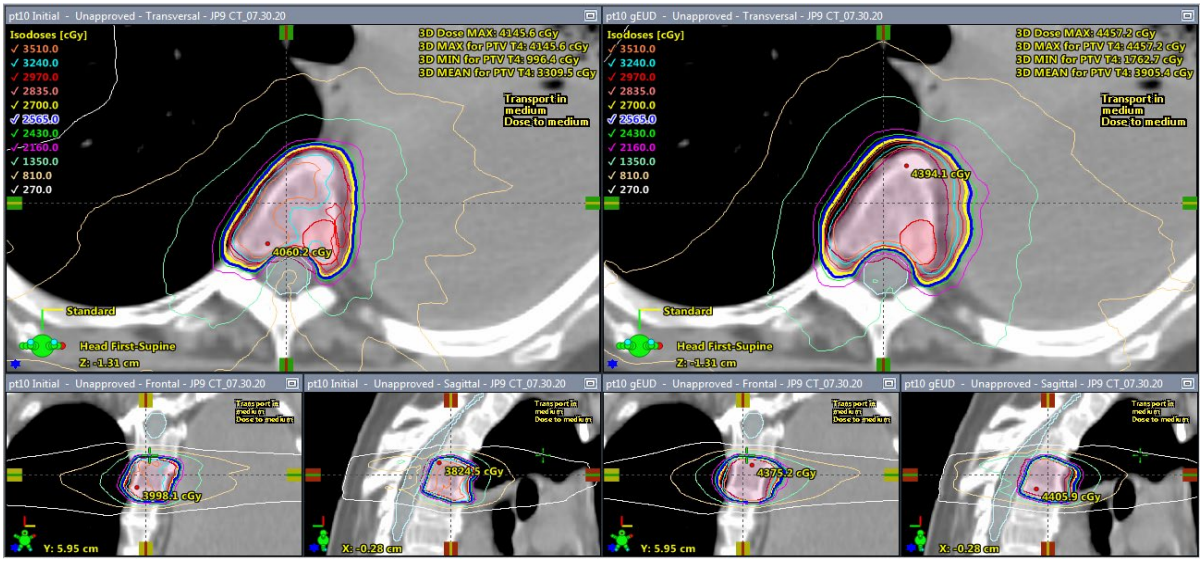


Figure 11: DVH - PTV coverage - DV plan (triangle) versus gEUD plan (square)