Enhancing target dose conformity while effectively sparing the spinal cord in proton arc treatment plans for cervical chordomas and chondrosarcomas

Jon Blalock, MS[*†], Jiyeon Park, PhD, DABR[†], Emilie Soisson, PhD, DABR[*], Kristen Vu, M.S., CMD, RT(T)[*]

[*]Grand Valley State University, Grand Rapids, Michigan

[†]University of Florida Health Proton Therapy Institute, Jacksonville, Florida

Abstract

Cervical spinal chordomas and chondrosarcomas present significant therapeutic challenges due to their proximity to the spinal cord and resistance to conventional radiotherapy. This retrospective study investigated the capability of proton arc therapy (PAT) to maintain or improve adequate target coverage while reducing dose to the spinal cord for cervical spinal chordomas and chondrosarcomas over standard fixed beam intensity modulated proton therapy (IMPT). While both IMPT and PAT use pencil beam scanning (PBS) to with energy modulation to deliver dose in discrete layers, IMPT relies on a limited number of fixed beam angles, whereas PAT delivers dose over an arc trajectory. Twelve adult cases of cervical spinal chordomas/chondrosarcomas that were previously treated with standard 3-4 field IMPT proton beams were selected and replanned with proton arc therapy. Proton arc therapy demonstrated superior spinal cord sparing and favorable linear energy transfer (LET) distributions compared to conventional IMPT. The McNamara model, based on the most comprehensive in vitro dataset to date, was used to estimate variable RBE values in this study, allowing for a more biologically accurate representation of spinal cord dose by incorporating LET and tissue-specific α/β ratios. Based on DVH analysis of the PAT replanned cases, the average spinal cord D0.1cc dose was reduced by 11.4% using a fixed RBE of 1.1 and by 11.6% using the McNamara variable RBE model. PAT also maintained roughly equivalent values for the prescription dose conformity indices. Robustness was evaluated with 3 mm isotropic setup uncertainty and 3.5% density uncertainty to ensure coverage and spinal cord constraints were met. These dosimetric advantages suggest that PAT could allow for dose escalation and reduced risk of late toxicities to these anatomically challenging cases.

Introduction

Spinal chordomas and chondrosarcomas are rare tumors that develop at the skull base and around the axial skeleton. While these tumors are histologically distinct, they share many features such as anatomic location and clinical presentation and are frequently evaluated together in the context of radiation therapy. Radiation therapy often plays a crucial role for local control and prevention of recurrence in these cases since the tumor location often limits the viability of surgical resection[1,2]. Due to the high rate of local failures, these targets may benefit from dose escalation if normal tissue toxicities can be adequately managed[3,4]. Particle-based modalities, such as proton or carbon ion therapy, can offer superior conformity and organ sparing compared to photon-based therapy, which results in increased local control and 5 year overall survival rates for skull base chordoma cases[2]. However, in many postoperative cases, the presence of metallic medical implants can compromise range accuracy and reduce plan robustness. As a result, it is a common planning practice to avoid the hardware with the proton beam, which limits beam angle selection.

This study seeks to investigate the feasibility of improving or maintaining adequate target dose coverage while effectively sparing the spinal cord using proton arc therapy (PAT) in treatment plans for cervical spinal chordomas and chondrosarcomas. Observed dosimetric improvements may support consideration of target dose escalation provided spinal cord constraints are maintained. PAT is a new and evolving treatment modality that has potential for reducing dose to OARs while maintaining similar coverage as compared to standard intensity modulated proton therapy (IMPT) treatments. One study observed that PAT outperformed IMPT and photon-based treatments with reduced normal tissue complication probability while maintaining similar target coverage in oropharyngeal cancer cases[5,6]. Similarly, recent studies have shown that PAT exhibits better target coverage, reduced dose to OARs, and improved robustness for breast cases compared to IMPT[7].

In addition to the issues mentioned previously, skull base tumors are a challenging site to treat with proton due to tissue inhomogeneities, restricted beam angle selection, and questionable relative biological effect (RBE) values because of variable linear energy transfer (LET)

distributions for tissues at the distal end of the beam path. PAT has been shown to have improved LET distributions with increased LET inside target volumes and decreased LET values in critical structures, potentially reducing the risk of relative biological effectiveness (RBE) driven toxicities[8,9]. A study has shown relative RBE enhancement associated with increased LET in targets (as well as overlapping critical structures) via geometry-based energy selection in PAT plans for ependymoma cases[10]. Proton therapy already sees much less integral dose than photon-based treatments due to the lack of exit dose, but this effect may be even more pronounced with PAT since there is much less overlapping of entrance dose compared to standard IMPT beam arrangements[11]. Many of these patients have implanted metallic hardware, which typically must be avoided by proton beams to prevent dose perturbations and uncertainties caused by interactions with the metal. This requirement significantly limits beam angle selection and complicates treatment planning and delivery for IMPT. With these challenges considered, proton arc therapy could prove to solve some of the problems of robustness with standard IMPT plans.

Methods and Materials

A retrospective study was performed using data collected from previously treated cervical spinal chordoma and chondrosarcoma patients. Approximately 12 adult cases previously treated with a combination of photon-based volumetric modulated radiation therapy (VMAT) and 3-4 field IMPT plans were selected. The use of a combination of photon and PBS modalities is a common institutional practice, particularly in critical areas, to address robustness issues associated with proton treatments. Since the tradeoffs between photon and IMPT treatments for these cases are already well documented, it is only of interest to compare the proton component of the previous treatments with an appropriately scaled PAT comparison plan to match the intended prescription and OAR dose contributions. For the purpose of maintaining confidentiality, all patient data was anonymized. This study maintained compliance with institutional review board policies, thereby ensuring ethical patient data handling.

The treatment planning system (TPS) used for the generation of the PAT plans was RayStation 2023B ARC Developer Tool Kit (RaySearch Laboratories, Stockholm, Sweden). This

TPS made use of the Monte Carlo dose calculation algorithm. The patients were planned on the IBA ProteusONE single-room pencil beam scanning system. The standard RBE calculation using the accepted value of 1.1 for protons relative to photons was performed. In addition, values were also obtained using the McNamara phenomenological RBE model to account for variation in RBE based on dose averaged LET (LET_d) and α/β ratios of the tissues of interest[12]. The model states,

$$RBE_{max}[LET_d, (\alpha/\beta)_x] = 0.843 + 0.154 \frac{2.686}{(\alpha/\beta)_x} LET_d$$

$$RBE_{min}[LET_d, (\alpha/\beta)_x] = 1.09 + 0.006 \frac{2.686}{(\alpha/\beta)_x} LET_d.$$

Literature suggests that this tumor type exhibits an α/β ratio of approximately 2-3 Gy[13,14]. Likewise, the spinal cord also has a reported α/β ratio of roughly 3-4 Gy[15]. For this reason, a global α/β ratio value of 3Gy was used for all tissues. A script was developed to calculate the RBE values from the model from the LET_d distribution and user input α/β ratio. Within the RayStation 2023B Arc Developer Tool Kit, two arc delivery options are available. One mode operates at a continuous speed delivering spots of only one energy layer per angle. The other mode instead takes more of a "step and shoot" approach and delivers spots at multiple energy layers before moving to the next angle. While the former method may be more ideal for efficiency and shorter delivery times, the discrete arc "step and shoot" method provides more insight into the full capabilities of this technique and thus was selected for this study.

Global settings, beam optimization parameters, and optimization objectives were kept as similar as possible by copying the clinical IMPT plan and changing the modality to proton arc. This way all beam parameters and optimization objectives were retained in the PAT plan. The number of ions per spot was set to 50,000. The Monte Carlo optimization algorithm was used with an uncertainty setting of 0.5%. The discrete arcs used 5 energy filtrations to coarsely bin energies. The robust optimization settings were defined with an isotropic setup uncertainty of 3mm, and a density uncertainty of 3.5%, which gave a total of 147 scenarios (each permutation of parameters gives a scenario, e.g. 1 mm superior-inferior, -1 mm right-left, 0 mm anterior-posterior, +3.5% density shift gives one possible scenario). The spinal cord max dose was

assigned as a robust objective which uses the defined robust optimization settings to tell the optimization algorithm to meet the dose constraint across all defined scenarios. The original IMPT plans typically consist of 4 beams arranged with two anterior oblique fields and two posterior oblique fields. For the PAT plans, two partial arcs with a length of 210 degrees were used. Objectives that did not apply to the arc plan such as minimum dose contributions per beam were removed. Otherwise, optimization objectives were kept the same between the plans. Metal hardware avoidance was also kept the same between the IMPT and PAT plans so that beam entry through the metal would be prohibited.

After generating an acceptable arc plan, comparisons were made. CTV D95% dose coverage and spinal cord D0.1cc dose were the metrics of most interest since the spinal cord is the dose limiting organ for this site. The initial optimization for the PAT plans showed increased coverage and roughly equal spinal cord doses with the clinical IMPT plans. Since objectives were kept consistent from the IMPT plan to the PAT plan, this meant the optimization algorithm had no trouble meeting the spinal cord dose and was able to fill in some dose that was sacrificed in the target volume for the clinical plan. The goal with further optimizations of the PAT plan was to lower the spinal cord dose constraint until target coverage was degraded until equal or slightly better than the clinically accepted IMPT plan that was used for treatment. This method allowed for a cohesive picture of PAT's spinal cord sparing capabilities across all the cases regardless of prescription dose or fractionation via the therapeutic ratio (CTV D95%/SC D0,1cc). Conformity, homogeneity, and LET/RBE were also of interest since these values help give a more complete picture of PAT's potential in creating a high-quality plan and improving patient outcomes.

Results

Spinal cord dose

Like the effect VMAT has in comparison to 3DCRT, arc therapy achieves similar coverage goals while greatly reducing high dose spillage into normal tissues. The average spinal cord D0.1cc assuming the standard RBE value of 1.1 was determined to be reduced by 11.4%

(WSR, $P = 0.002$) for the PAT plans compared to the IMPT plans. Likewise, using the McNamara model to estimate variable RBE values which take LET into account, the average spinal cord D0.1cc was reduced by 11.6% (WSR, $P = 0.002$) for the PAT plans.

LET considerations

The spinal cord average LET and LET at 1cc were found to be reduced in the arc plans by 0.38keV/μm and 0.91keV/μm respectively, corresponding to reductions of 11.9% (T-test, $P < 0.001$) and 14.7% (WSR, $P = 0.004$). This potentially could indicate PAT may be better suited to prevent late toxicities from any unexpected dose enhancement in surrounding tissue.

Therapeutic ratio and conformity

Since prescription doses varied across cases, it is of value to consider a ratio of target coverage to spinal cord dose CTV D95%/SC D0.1cc. The PAT plans showed a 14.1% increase in this ratio (WSR, $P = 0.002$). Conformity was evaluated using the Van't Riet conformity index equation,

$$CI = \frac{TV_{95}^2}{(TV)(V_{95})}$$

where TV_{95} is the target volume covered by 95% of the prescription dose, TV is the total target volume, and V_{95} is the total volume covered by 95% of the prescription dose. This formulation of the conformity index was chosen since it penalizes under coverage as well as dose spillage into healthy tissue. The observed mean CI for the CTVs was 0.569 for the IMPT plans and 0.568 for the PAT plans. The mean CI for the PTVs was 0.756 for the IMPT plans and 0.776 for the PAT plans. However, these results were not statistically significant, indicating conformity between IMPT and PAT was comparable.

Discussion

Summary

The results of this study confirm that proton arc therapy has potential to improve the therapeutic ratio for cervical spinal chordoma and chondrosarcoma patients. In this study's

cohort, the average spinal cord D0.1cc was reduced by 11.4% with the standard 1.1 RBE model, and 11.6% with the McNamara model, both with statistical significance (WSR, $P = 0.002$ for both 1.1 RBE and McNamara). Target coverage was maintained or slightly improved with PAT compared to the IMPT plans. These dosimetric advantages are due to the increased dose modulation options when given more degrees of freedom in beam angle selection within the arc given that the settings and optimization objectives were kept consistent. These findings align with prior works which highlight PAT's ability to enhance treatment of anatomically or geometrically complex regions including brain, breast, and oropharyngeal cancers. Incorporating LET and RBE considerations adds further biological validity to the dosimetric advantage of PAT. The observed average LET reduction of 11.9% (T-test, $P < 0.001$) and 14.7% (WSR, $P = 0.004$) at 1cc within the spinal cord suggests potential for lower risk of toxicities, especially when distal LET hot spots can be mitigated. Range and setup variability were accounted for by using robust optimization objectives which ensured coverage and spinal cord constraints were maintained across multiple uncertainty scenarios. PAT showed a 14.1% (WSR, $P = 0.002$) increase in the therapeutic ratio (CTV D95%/SC D0.1cc). The CI difference between IMPT and PAT was not statistically significant, which signifies they were of similar magnitude.

Clinical implications

The magnitude of spinal cord dose reduction observed in this study could potentially translate to meaningful clinical impact. The 11-12% average max dose reduction could further highlight the safe delivery of the current plan prescriptions or even advocate for dose escalation strategies given established dose response relationships for spinal cord tolerance. This corresponds to a 5-6 Gy max dose reduction if, for example, the spinal cord is at the maximum dose constraint of 50 Gy as stated in QUANTEC[16]. Given that local control rates for chordomas and chondrosarcomas are suboptimal with conventional doses, and they exhibit considerable radioresistance, the ability to escalate safely could be a significant improvement for patient outcomes. The improved therapeutic ratio of 14.1% suggests that PAT could facilitate escalation of almost 10Gy for a prescription of 70Gy for example (typical chordoma prescriptions range

from around 70-80 Gy)[17]. In addition, the reduction of LET hotspots in critical structures may be especially important for patients with longer life expectancies where late effects become increasingly relevant. By spreading out the high LET distal end points of the proton beams, unexpected biological responses can be further avoided.

Limitations and future improvements

As this study features emergent technology and a rare type of tumor, it had a relatively small sample size. In addition, many of these patients have surgical hardware which must be avoided during proton treatment due to range uncertainties or a degradation of robustness. Also, it being a retrospective study and not entirely based on clinical outcomes, it is subject to bias. However, it is for this reason that the study kept a standard two arc beam set and all relevant optimization objectives used in the clinical treatment plan consistent. The "step and shoot" discrete arc technique may not excel from a clinical workflow standpoint. A continuous arc may provide significant reductions in overall treatment time, which could be valuable for patient comfort and positioning reliability. However, discrete arc has the advantage of being able to deliver multiple energy layers per angle. The discrete arc mode also provides the planner with a table of monitor units used per beam angle like how most treatment planning systems show the monitor units used per segment of an IMRT plan. An initial PAT optimization may help planners identify optimal angles from this monitor unit weighting data when trying to find ideal beam geometry for an IMPT plan.

Conclusion

This study demonstrates that proton arc therapy can significantly reduce spinal cord max dose and LET while maintaining or improving target coverage in the treatment of cervical spinal chordomas and chondrosarcoma. The improvement of the therapeutic ratio could potentially allow for dose escalation or highlight the reduced toxicity PAT can achieve for these challenging cases. By taking advantage of arc geometry, PAT offers promising advancements over conventional IMPT treatments for this site. The biological advantages, demonstrated through

reductions in LET in the spinal cord and the McNamara variable RBE model-based dose, suggest potential for PAT to incur decreased late toxicity risks. This is especially important for patients with favorable prognoses who may experience long-term survivorship. The successful implementation of PAT while maintaining metallic hardware avoidance constraints demonstrates its feasibility even in complex post-operative scenarios. These findings further support efforts being made for other treatment sites and help paint a cohesive picture of the therapeutic potential presented by PAT. As technology advances and a cohesive body of evidence is formed for PAT, it may become the new standard of care in treating chordomas and chondrosarcomas amongst many other challenging sites.

Declaration of Generative AI and AI-assisted technologies in the writing process- During the preparation of this work the author(s) used Chat GPT and Claude to assist with content organization, language refinement, and figure formatting. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Tables and Figures

Table 1. Key data summary

Case	Plan Type	Dose Metrics (cGy)			LET (keV/μm)		Conformity Index		Target Coverage Ratio
		CTV D95%	Spinal Cord D0.1cc (1.1 RBE)	Spinal Cord D0.1cc (McNamara RBE)	CTV Avg LET	Spinal Cord Avg LET	CI CTV	CI PTV	
1	Clinical	2571	2277	2416	2.6	3.1	0.460	0.773	1.129
	Arc	2581	1935 (↓15.0%)	2063	2.6	2.8	0.433	0.759	1.334 (↑18.1%)
2	Clinical	2258	2129	2243	2.5	3.3	0.413	0.748	1.061
	Arc	2322	2021 (↓4.7%)	2156	2.6	3	0.414	0.775	1.149 (↑8.3%)
3	Clinical	1595	1409	1562	2.9	3.3	0.603	0.867	1.132
	Arc	1623	1230 (↓12.7%)	1351	2.6	2.5	0.574	0.803	1.320 (↑16.6%)
4	Clinical	1379	1397	1509	2.9	3.2	0.556	0.788	0.987
	Arc	1520	1346 (↓3.7%)	1481	2.6	3	0.536	0.813	1.129 (↑14.4%)
5	Clinical	2157	1816	2083	3	3.1	0.730	0.822	1.166
	Arc	2095	1583 (↓12.8%)	1712	2.8	2.4	0.702	0.861	1.323 (↑13.5%)
6	Clinical	2157	2064	2282	2.7	3.6	0.687	0.779	1.045
	Arc	2045	1587 (↓23.1%)	1750	2.7	2.9	0.683	0.827	1.289 (↑23.3%)
7	Clinical	1350	1178	1283	2.5	2.5	0.490	0.717	1.146
	Arc	1311	1092 (↓7.3%)	1195	2.6	2.5	0.530	0.762	1.201 (↑4.8%)
8	Clinical	1741	1632	1808	3	3.2	0.318	0.518	1.067
	Arc	1884	1503 (↓7.9%)	1722	2.3	2.8	0.379	0.569	1.175 (↑10.2%)
9	Clinical	1361	1182	1283	2.8	2.9	0.738	0.815	1.151
	Arc	1366	1028 (↓13.0%)	1109	2.6	2.9	0.730	0.846	1.319 (↑14.6%)
10	Clinical	1338	1174	1295	2.9	3.3	0.593	0.732	1.140
	Arc	1341	1009 (↓14.1%)	1095	2.7	3	0.659	0.822	1.329 (↑16.6%)
11	Clinical	1327	1174	1271	2.7	2.9	0.650	0.760	1.136
	Arc	1352	1071 (↓8.8%)	1151	2.7	2.6	0.611	0.762	1.263 (↑11.7%)
12	Clinical	1329	1170	1271	2.6	3.3	0.598	0.747	1.136
	Arc	1358	1077 (↓7.9%)	1168	2.8	2.8	0.560	0.719	1.253 (↑10.4%)

Figure 1. Spinal Cord Dose Reduction (1.1 RBE & McNamara)

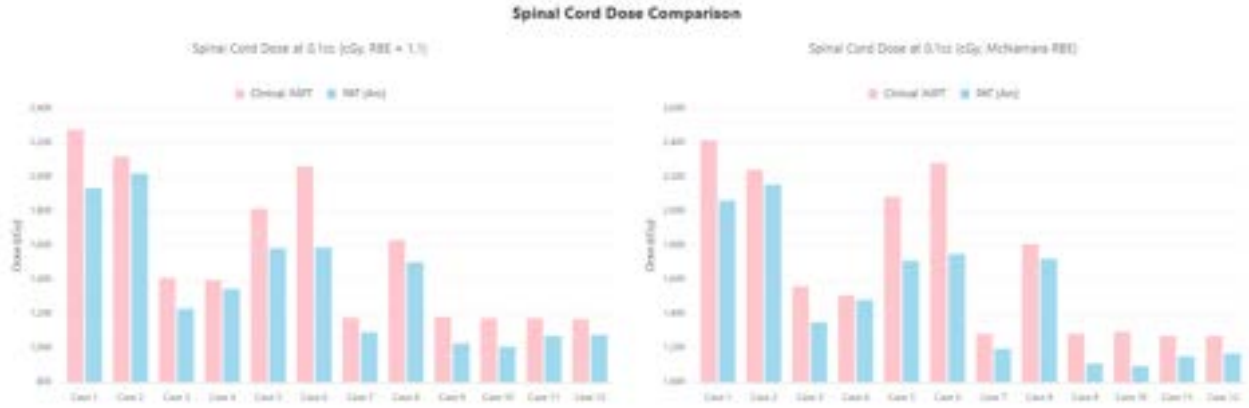


Figure 2. Avg LET (CTV & Spinal Cord)

Figure 3. Conformity Index Comparison (CTV & PTV)

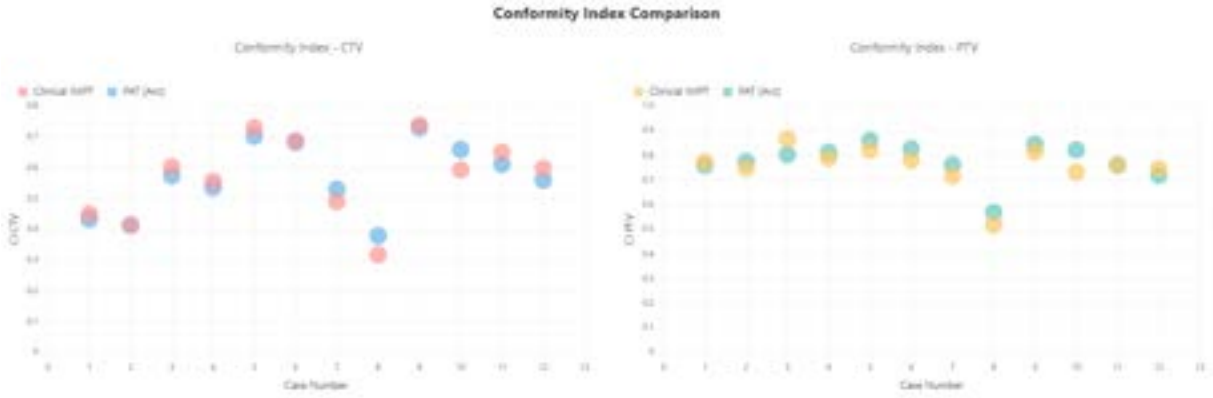


Figure 4. Therapeutic Ratio (CTV D95%/SC D0.1cc)

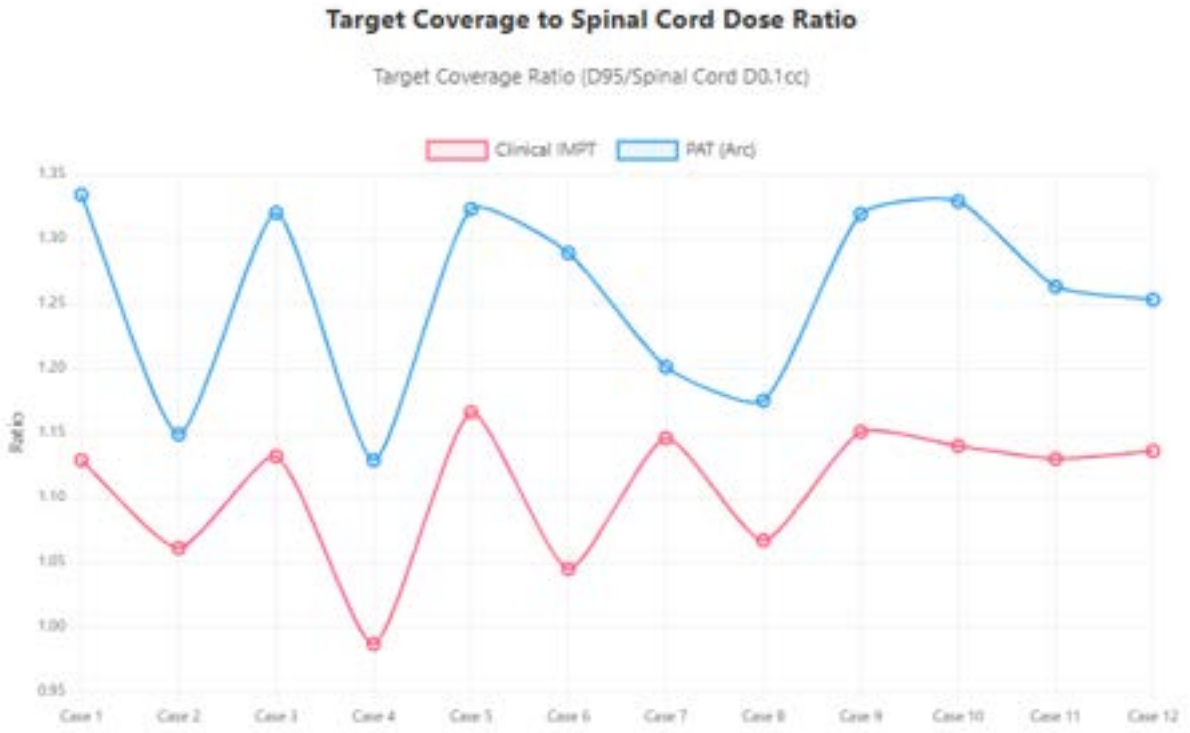
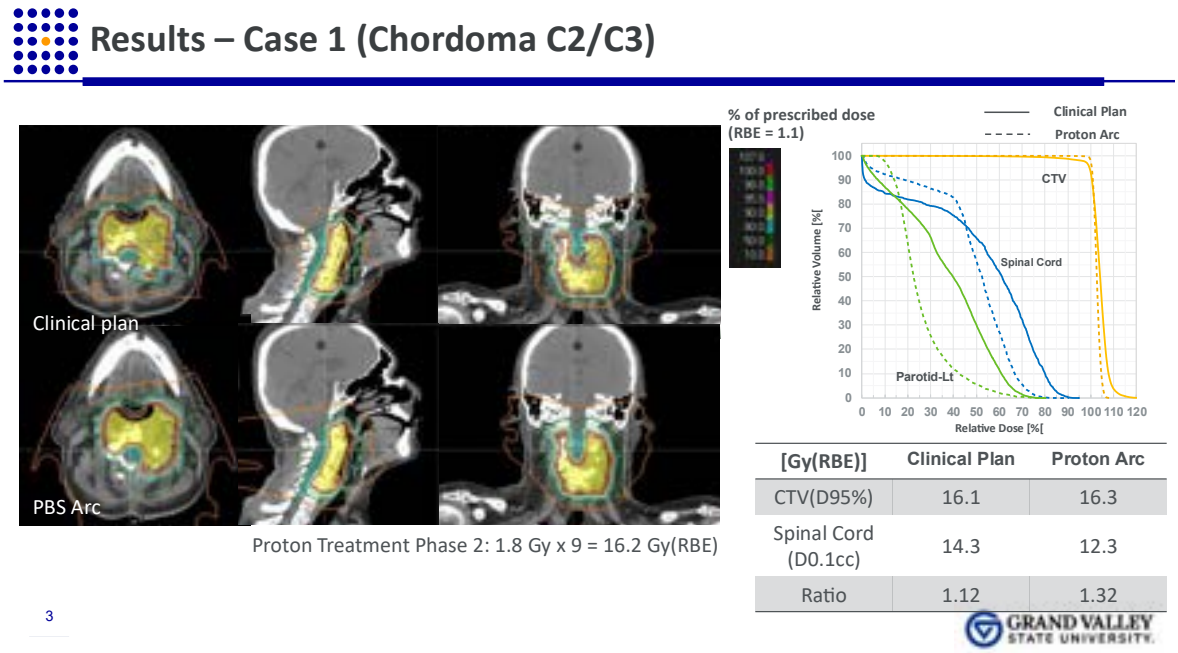
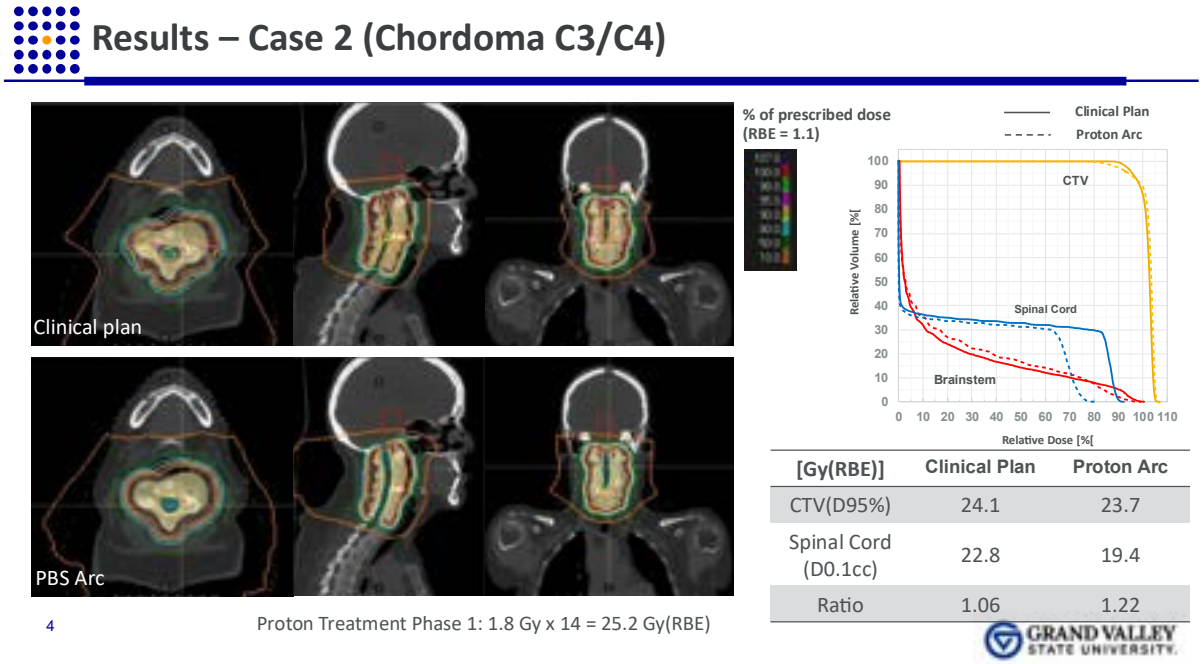


Figure 5. Dose Distribution (Case 1)



[Gy(RBE)]	Clinical Plan	Proton Arc
CTV(D95%)	16.1	16.3
Spinal Cord (D0.1cc)	14.3	12.3
Ratio	1.12	1.32

Figure 6. Dose Distribution (Case 2)



[Gy(RBE)]	Clinical Plan	Proton Arc
CTV(D95%)	24.1	23.7
Spinal Cord (D0.1cc)	22.8	19.4
Ratio	1.06	1.22

Figure 7. LET_d Distribution, IMPT (left), PAT (right)

LETd comparison in spinal cord (with dose threshold ≥ 80% of Rx)

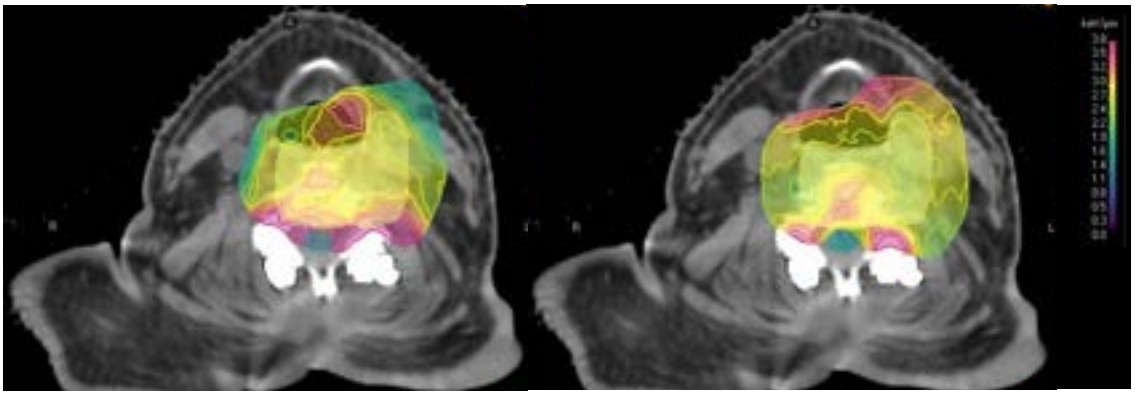


Figure 8. Spinal Cord Sparing Statistical Results

T-test for the spinal cord dose sparing (RBE = 1.1) based on the normal distribution (Shapiro-Wilk test) for both P< 0.05

RBE = 1.1
RBE = McNamara,

Average saving 11% in RBE = 1.1
Average saving 12% in RBE – McNamara Model using LET

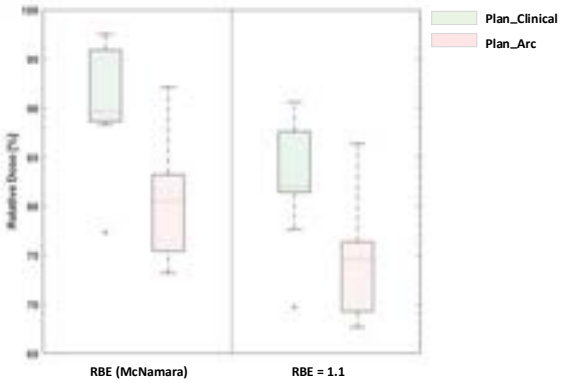


Figure 9. Therapeutic Ratio Statistical Results

Wilkinson signed rank test
Target Coverage (D95)/SpinalCord D0.1cc (RBE = 1.1), $p<0.05$

Average and max LET both showed $p<0.05$