

The Role of Plan Robustness Evaluation in Comparing Protons and Photons Plans - An Application on IMPT and IMRT Plans in Skull Base Chordomas

Manthala Padannayil Noufal, Lamberto Widesott¹, Shamurailatpam Dayananda Sharma, Roberto Righetto¹, Marco Cianchetti¹, Marco Schwarz^{1,2}

Department of Medical Physics, Apollo Proton Cancer Centre, Chennai, Tamil Nadu, India, ¹Department of Proton Therapy, Azienda Provinciale Per I Servizi Sanitari, ²TIFPA - INFN, Trento, Italy

Abstract

Purpose: To analyze robustness of treatment plans optimized using different approaches in intensity modulated proton therapy (IMPT) and investigate the necessity of robust optimization and evaluation in intensity modulated radiotherapy (IMRT) plans for skull base chordomas. **Materials and Methods:** Two photon plans, standard IMRT and robustly optimized IMRT (RB-IMRT), and two IMPT plans, robustly optimized multi field optimization (MFO) and hybrid-MFO (HB-MFO), were created in RayStation TPS for five patients previously treated using single field uniform optimization (SFO). Both set-up and range uncertainties were incorporated during robust optimization of IMPT plans whereas only set-up uncertainty was used in RB-IMRT. The dosimetric outcomes from the five planning techniques were compared for every patient using standard dose volume indices and integral dose (ID) estimated for target and organs at risk (OARs). Robustness of each treatment plan was assessed by introducing set-up uncertainties of ± 3 mm along the three translational axes and, only in protons, an additional range uncertainty of $\pm 3.5\%$. **Results:** All the five nominal plans provided comparable and clinically acceptable target coverage. In comparison to nominal plans, worst case decrease in $D_{95\%}$ of clinical target volume-high risk (CTV-HR) were 11.1%, 13.5%, and 13.6% for SFO, MFO, and HB-MFO plans respectively. The corresponding values were 13.7% for standard IMRT which improved to 11.5% for RB-IMRT. The worst case increase in high dose ($D_{1\%}$) to CTV-HR was highest in IMRT (2.1%) and lowest in SFO (0.7%) plans. Moreover, IMRT showed worst case increases in $D_{1\%}$ for all neurological OARs and were lowest for SFO plans. The worst case $D_{1\%}$ for brainstem, chiasm, spinal cord, optic nerves, and temporal lobes were increased by 29%, 41%, 30%, 41% and 14% for IMRT and 18%, 21%, 21%, 24%, and 7% for SFO plans, respectively. In comparison to IMRT, RB-IMRT improved $D_{1\%}$ of all neurological OARs ranging from 5% to 14% in worst case scenarios. **Conclusion:** Based on the five cases presented in the current study, all proton planning techniques (SFO, MFO and HB-MFO) were robust both for target coverage and OARs sparing. Standard IMRT plans were less robust than proton plans in regards to high doses to neurological OARs. However, robust optimization applied to IMRT resulted in improved robustness in both target coverage and high doses to OARs. Robustness evaluation may be considered as a part of plan evaluation procedure even in IMRT.

Keywords: Chordomas, integral dose, Intensity-modulated proton therapy, intensity-modulated radiotherapy, proton beam therapy, robust evaluation, robust optimization

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INTRODUCTION

Proton beam therapy (PBT), specially using pencil beam scanning (PBS) technique, is increasingly adopted as a superior radiotherapy technique, because of its better sparing of surrounding normal tissues and reduction of integral dose (ID).^[1,2] Several studies have reported an improved quality of life^[3,4] and reduction of radiation-induced cancer after treatment with PBT.^[5,6] PBT is considered as the most

appropriate treatment for complex and radio-resistant tumors, with 3-years survival reported at 91% for chordomas and

Address for correspondence: Dr. Manthala Padannayil Noufal, Department of Medical Physics, Apollo Proton Cancer Centre, 100 Feet Road Tharamani, Chennai - 400 053, Tamil Nadu, India. E-mail: noufalsh@gmail.com

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7-year survivals of 94% for chondrosarcoma.^[7,8] These patients were treated with proton double scattering (DS) technique alone or in combination with photon radiotherapy. In general, treatment planning of skull base chordoma is complex due to its proximity to many critical organs such as optic nerves, brainstem, optic chiasm, cranial nerves, cochlea, and temporal lobes. Quite often these organs at risk (OARs) abut with the target and few OARs can even be within the concavity of the target. Thus, the treatment planning for chordoma poses unique challenges, due to a) the very high dose (72-74 Gy) required for an optimal tumor control, b) the dose constrains to the surrounding OARs.

Intensity-modulated proton therapy (IMPT) plans allows optimization of proton spots, weights, and ranges to achieve a highly conformal dose distribution to complex targets such as chordoma. IMPT can be designed either by using single field optimization (SFO) or multi field optimization (MFO). SFO plans are optimized to deliver a homogeneous dose to the target from each field. On the other hand, MFO proton plans rely on delivery of non-uniform doses from each fields and can potentially reduce dose to OARs located within the concavity of the target.^[9,10] The IMPT plans, especially MFO, are more susceptible to set-up and proton range uncertainty.^[9-11] The traditional concept of optimization based on planning target volume (PTV) and planning organ at risk volume (PRV) is discouraged in IMPT planning due to lack of robustness especially for complex clinical sites such as chordomas.^[9] Robust optimization has been suggested as a method to potentially solve the PTV/PRV limitations, for improved and robust clinical target volume (CTV) coverage and OARs sparing, for both photon and proton treatments.^[9-15] A shortcoming of robust optimization is the calculation time which, especially when using Monte Carlo (MC) dose calculation algorithms, might increase significantly. Trento proton therapy center, recently introduced a hybrid-MFO (HB-MFO) approach in proton planning, wherein PTV is generated only to compensate set-up errors, followed by robust optimization, with respect to range errors, on such PTV.^[11] This approach has been selected to minimize the number of scenarios to be considered during the optimization process. However, it is not known which proton planning technique is most efficient and robust.

On the other hand, traditional intensity-modulated radiotherapy (IMRT) plans are always optimized to PTV to deliver at least 95% of the prescription dose to CTV, in all possible set-up error uncertainties encountered during the treatment. As much as the “margin recipe,” for example, proposed by van Herk,^[16] represented a significant step ahead in the inclusion of geometrical uncertainties in the planning procedures, it is a first approximation rather than a complete solution to the problem. An explicit inclusion of geometrical uncertainties in the optimization procedures (“robust optimization”) for photons may provide a more complete approach to find the right balance between target coverage and OAR sparing. As a consequence, it is interesting to compare protons and photons dose distributions when they

are optimized with the same approach, and robustness is also explicitly evaluated on the final plan.

Robust optimization has been studied for photon volumetric modulated arc therapy (VMAT) to mitigate motion and set-up error in carcinoma lung and breast.^[14,15] However, dosimetric impact of robust optimization has not been reported for chordomas treated with fixed field IMRT. Moreover, to the best of our knowledge, no study has been conducted to evaluate the robustness and efficiency of IMRT and IMPT plans in the same patient dataset. This paper compares SFO, MFO, and HB-MFO in skull base chordomas. Furthermore, the dosimetric impact of robust optimization in fixed field IMRT plans were investigated on the same patient datasets.

MATERIALS AND METHODS

Treatment planning

Five skull base chordoma patients, previously treated at Trento proton therapy center using proton SFO technique, were selected for this retrospective dosimetric study. RayStation-v6.0 (RaySearch Laboratories, Stockholm, Sweden) treatment planning system (TPS) was used for contouring, optimization, and dose computation. In four of the five patients (A-D), two CTVs were delineated - CTV high risk (CTV-HR) and CTV low risk (CTV-LR) - while in the case of patient E only CTV-HR was defined. PTVs were generated with 4 mm isotropic margins around the corresponding CTVs: such isotropic expansion was obtained by taking into consideration the patient’s positioning procedures in place and range uncertainties reported in the literature.^[17] The PRVs were generated by growing 2 mm isotropic margins around the corresponding OARs. Patients A, B, C, D were sequentially planned for a dose of 54 Gy RBE to CTV-LR, followed by a boost dose of 20 Gy RBE to CTV-HR. Whereas, patient E was planned for a total dose of 72 Gy RBE to CTV-HR. Treatment plans were optimized to cover 98% volume of the CTVs by 95% of the prescribed dose, while dose to PRVs were optimized to maintain clinical goals compliance for OARs [Table 1].

Photon plans

For each patient two photon based IMRT plans - nonrobustly optimized IMRT (IMRT) and robustly optimized IMRT (RB-IMRT) - were created in the TPS. IMRT plans were generated using 6 MV X-rays from True Beam linac (Varian Medical Systems) equipped with Millennium 120 MLC. In all patients, nine equally spaced fixed coplanar fields were used, except for Patient-A, who received eight coplanar and one non-coplanar beams. In each IMRT plan, PTVs were optimized for target coverage and PRVs were optimized for OAR sparing. In RB-IMRT, CTVs and OARs were robustly optimized by introducing ± 5 mm set-up uncertainty on one axis at a time (i.e., (5mm, 0, 0), (0, 5mm, 0), (0, 0, 5mm), (-5mm, 0, 0) etc.), using mini-max based robust optimization tool available in the TPS.^[10] Finally, the dose computation was performed using the collapse cone algorithm.

Proton plans

Three proton plans (SFO, MFO, and HB-MFO) were optimized in the TPS for each patient. All proton treatment plans were simulated in the TPS for Proteus Plus (IBA, Louvain La Neuve, Belgium) proton therapy system equipped with dedicated pencil beam nozzle capable of delivering 70 to 230 MeV proton energy. The detailed characteristics of the Proteus Plus used in this study are described elsewhere.^[18-20] Beam arrangement used in proton plans is described in Table 2. In SFO technique, each beam is individually optimized to deliver uniform dose to PTV which is at a margin of 4 mm from the CTV. The MFO plans were robustly optimized for CTVs, with ± 5 mm set-up uncertainty on one translational axis at a time and a range uncertainty of 3.5%. In hybrid MFO technique, the CTV to PTV margin was reduced to 3 mm; this PTV was robustly optimized only for the range uncertainties of 3.5%. Details of the HB-MFO approach can be found in the paper by Tommasino *et al.*^[11] In every proton plan, robust optimization was performed using the same mini-max approach applied for the photon planning,^[10] whereas final dose was computed with the MC algorithm available in TPS.

Plan quality and integral dose evaluation

The dosimetric outcome of the five (3 proton, 2 photon) competing nominal plans of every patient were compared using standard dose volume indices derived from the cumulative dose volume histogram (DVH). For every plan, target coverage was reported as dose to x% of the volume ($D_{x\%}$) (i.e. $D_{98\%}$ and $D_{95\%}$) while hot spots were reported as $D_{1\%}$. The maximum dose to all serial OARs were evaluated as $D_{1\%}$ for the brainstem, chiasm, spinal cord, optic nerves and temporal lobes. In the case of cochlea D_{mean} was assessed for all plans to evaluate the plan quality. Moreover, in order to assess the low dose bath in all

techniques, ID was calculated for normal tissue, normal brain and other relevant OARs such as brain stem and temporal lobes in both proton and photon plans. ID can be computed as the product of the organ density, volume, and mean dose, using the equation:^[21]

$$ID_j = \rho_j V_j D_j$$

where ρ_j , V_j and D_j are the density, volume and mean dose of the organ respectively, for sub-volume j , assuming that the density of the organ is equal to its mean density and that all the sub-volumes of the organ received mean dose D .

Robust evaluation

The robustness of every photon and proton plan was evaluated using an in-house developed Python script. It enables us to create all possible error scenarios of both set-up and range uncertainties and accordingly study the perturbed dose distribution of the nominal plans. For the analysis, we decided not to use the same shifts we used for optimization. For each plan, 16 error scenarios were created by introducing set-up uncertainties of ± 3 mm along the three translational axes simultaneously, namely, the anterior-posterior (A-P), superior-inferior (S-I), and right-left (R-L) directions (i.e., 8 different shifts (3 mm, 3 mm, 3 mm) (-3 mm, 3 mm, 3 mm) (3 mm, -3 mm, 3 mm) etc., with the about same module of the vector used for optimization (i.e., $\sqrt{3^2 + 3^2 + 3^2} = 5.2$) and range uncertainties were incorporated by changing the CT number by $\pm 3.5\%$. This resulted in 16 dose distributions derived from each proton plan. While in IMRT plans, only set-up uncertainties were introduced with magnitude of ± 3 mm in all axes simultaneously, resulting in 8 dose distributions errors of the nominal IMRT plans. The corresponding DVH error dose distributions and nominal plans were exported to MATLAB (R2013a, The MathWorks, Natick, MA) for a final analysis. An in-house MATLAB code was written to analyze the DVHs obtained with the 16 simulated scenarios for robustness evaluation, aiming to find the worst decrease (i.e., the lowest value for the CTV $D_{98\%}$ or $D_{95\%}$ among the 16 scenarios simulated), worst increase (i.e., the highest value for the CTV or OARs $D_{1\%}$ among the 16 simulated scenarios) and mean dose for the cochlea (where the worst increase in the D_{mean} dose was assessed).

Table 1: Clinical goals for organ at risk

Structure	Clinical goals (Gy RBE) protons (Gy) photons
Brainstem	$D_{1\%} \leq 60$
Chiasm	$D_{1\%} \leq 55$
Spinal cord	$D_{1\%} \leq 55$
Optic nerve	$D_{1\%} \leq 55$
Temporal lobes	$D_{1\%} \leq 72$
Cochlea	$D_{mean} \leq 35$

RBE: Relative biological effectiveness

Table 2: Beam arrangements for proton plans (gantry and couch angles are given in degrees)

Name	Field-1		Field-2		Field-3		Field-4	
	Gantry	Couch	Gantry	Couch	Gantry	Couch	Gantry	Couch
Patient-A	70	350	120	5	240	355	290	10
Patient-B	80	350	110	350	250	10	280	10
Patient-C	80	0	110	350	250	10	280	0
Patient-D	70	90	90	330	270	30	-	-
Patient-E	70	0	100	330	260	30	290	0

RESULTS

Treatment plan evaluation

Figure 1 shows the spatial dose distribution obtained from the three nominal proton plans, namely SFO [Figure 1a], MFO [Figure 1b], HB-MFO [Figure 1c], and two photon

plans, IMRT [Figure 1d] and RB-IMRT [Figure 1e] for a representative patient. While the dose distributions from the three proton plans are similar, both photon plans showed significant increase in the intermediate to low dose to surrounding normal tissues. Table 3 represents the overall mean and standard deviation (SD) of $D_{98\%}$, $D_{95\%}$, and $D_{1\%}$

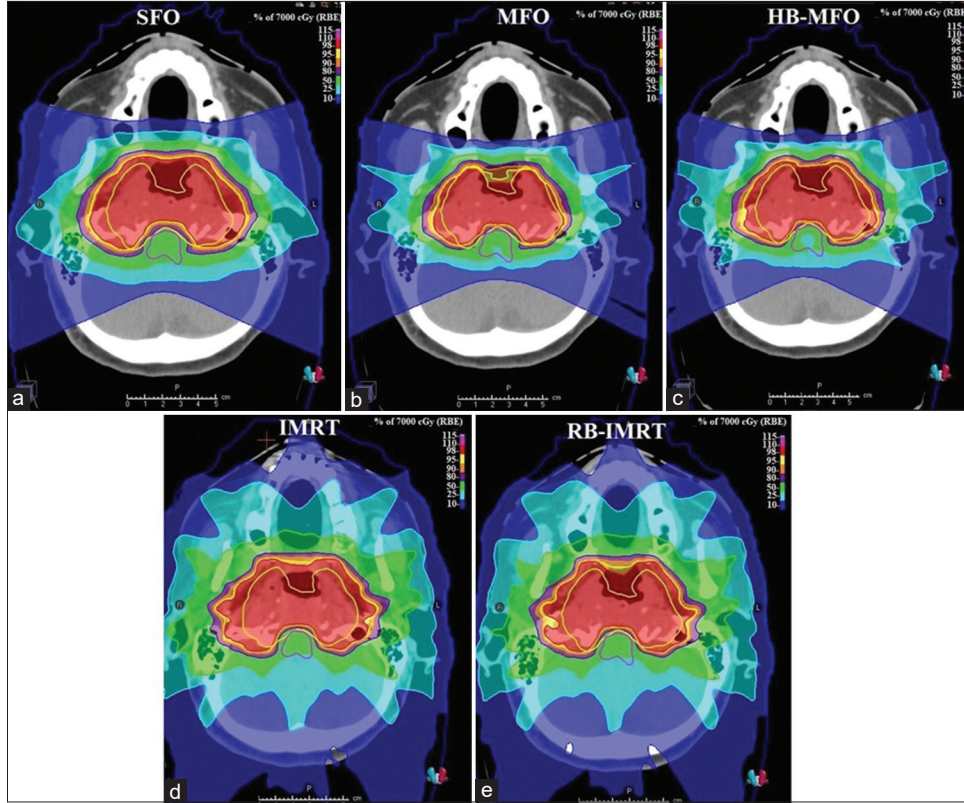


Figure 1: Dose distribution from the three proton plans, namely (a) SFO, (b) MFO, (c) HB-MFO and two photon plans (d) IMRT and (e) RB-IMRT for one of the representative patients

Table 3: The overall mean and standard deviation of dose to 98% ($D_{98\%}$), 95% ($D_{95\%}$), 1% ($D_{1\%}$) of clinical target volume high risk and clinical target volume low risk from the competing proton and photon plans of all five patient

Structure	Plans	$D_{98\%}$		$D_{95\%}$		$D_{1\%}$	
		(Gy RBE) protons		(Gy RBE) protons		(Gy RBE) protons	
		(Gy) photons	(Gy) photons	(Gy) photons	(Gy) photons	(Gy) photons	(Gy) photons
		Nominal	Worst Decrease	Nominal	Worst Decrease	Nominal	Worst Increase
CTV-HR	SFO	58.58±8.64	56.05±5.59	62.32±9.49	55.43±6.51	77.33±1.87	77.87±2.18
	MFO	61.73±6.57	56.04±6.27	65.44±6.66	56.63±6.64	78.50±3.08	79.99±3.43
	HB-MFO	63.01±7.57	56.86±6.63	66.70±7.06	57.60±7.15	78.42±3.01	79.38±2.67
	IMRT	60.94±9.99	52.06±5.32	64.99±8.08	56.06±7.42	79.37±3.86	81.07±4.09
	RB-IMRT	62.04±6.97	55.04±5.49	65.06±8.08	57.55±5.51	78.04±2.51	78.03±2.34
CTV-LR	SFO	52.46±3.88	50.09±2.26	53.54±3.21	50.74±3.18	57.53±2.15	58.12±3.12
	MFO	52.07±3.62	49.12±3.12	53.98±2.41	50.19±2.3	58.12±1.35	60.12±2.92
	HB-MFO	52.21±3.97	50.02±2.98	53.55±3.53	50.21±3.18	56.53±2.12	57.12±3.14
	IMRT	52.43±2.55	48.40±3.59	54.90±1.95	48.08±2.3	59.12±2.12	61.12±3.23
	RB-IMRT	52.12±3.44	50.14±3.13	53.23±2.19	50.12±2.49	56.15±2.14	58.12±3.32

CTV-HR: Clinical target volume-high risk, CTV-LR: Clinical target volume-low risk, SFO: Single field uniform optimization, MFO: Multi field optimization, HB-MFO: Hybrid-multi field optimization, IMRT: Intensity modulated radiotherapy, RB-IMRT: Robustly optimized-intensity modulated radiotherapy, RBE: Relative biological effectiveness

of CTV- HR and CTV-LR, from the competing proton and photon plans of all five patients. In agreement with our planning goal, all the nominal plans of both proton and photon provided similar target coverage and hot spot volume, except for SFO plans, which showed a slightly less dose to CTV-HR only with mean \pm SD $D_{98\%}$ and $D_{95\%}$ of 58.58 ± 8.64 and 62.32 ± 9.49 Gy RBE, respectively. In all the five plans, HB-MFO showed slightly better dose to CTV-HR with mean \pm SD of $D_{98\%}$ at 63.01 ± 7.57 Gy RBE and $D_{95\%}$ at 66.70 ± 7.06 Gy RBE in comparison to the other plans. The mean $D_{98\%}$, $D_{95\%}$ to CTV-LR remains similar in all five plans.

Robust evaluation for target

Figure 2 shows the nominal (red) and perturbed (blue) DVHs of a representative CTV-HR, resulted from the no-error and error introduced plans of SFO [Figure 2a], IMRT [Figure 2b] and RB-IMRT [Figure 2c] respectively. The wider spread of the shoulder and tail regions of the cumulative DVHs in IMRT plan depict lesser robustness in minimum coverage and maximum dose to CTV-HR. The worst case decrease in target coverage ($D_{98\%}$ and $D_{95\%}$) and worst case increase in high dose volume ($D_{1\%}$) resulted from the possible error scenarios simulated during robust evaluation is also depicted in Table 3. All the five competing plans except regular IMRT showed similar worst case mean $D_{98\%}$ ($55 < D_{98\%} < 57$ Gy RBE) and mean $D_{95\%}$ ($55 < D_{95\%} < 58$ Gy RBE) for CTV-HR. The regular IMRT plans showed lowest mean \pm SD $D_{98\%}$ of 52.06 ± 5.32 Gy RBE and largest mean \pm SD of $D_{1\%}$ of 81.07 ± 4.09 Gy RBE. Similar pattern of worst case decrease in mean $D_{98\%}$ and $D_{95\%}$ and increase of $D_{1\%}$ from IMRT was observed even for CTV-LR target. The worst case decrease in $D_{98\%}$ and $D_{95\%}$ of CTV-HR, compared to nominal plans, resulted in -4.3% and -11.1% for SFO, -9.2% and -13.5% for MFO, -9.8% and -13.6% for HB-MFO. The corresponding values from photon plans were -14.6 and -13.7% for standard IMRT, -11.3% and -11.5% for RB-IMRT respectively. The worst case increase in high dose ($D_{1\%}$) was highest in photon IMRT ($+2.1\%$) and lowest in SFO ($+0.7\%$) plan.

Robust evaluation for organs at risks

Figure 3 represents the results of the robustness evaluation for select neurological OARs; brainstem [Figure 3a], optic chiasm [Figure 3b], and optic nerves [Figure 3c] for the same representative patient. The red graphs represent the DVHs from the nominal plans while all the perturbed blue graphs are from error scenarios. Table 4 represents the maximum dose ($D_{1\%}$) related to serial organs and mean dose (D_{mean}) related to cochlea from the competing treatment plans and their worst case increase in $D_{1\%}$ ($WI-D_{1\%}$) and D_{mean} ($WI-D_{mean}$). The values represent the mean \pm SD from all five patients. All nominal treatment plans resulted in OAR doses within the prescribed tolerance limits. However, in the worst case scenario plans, OAR doses were higher than the prescribed tolerance limits. In the nominal plans, HB-MFO resulted lower $D_{1\%}$ for all serial OARs and least D_{mean} for cochlea than the competing plans. The worst case analysis showed IMRT plans were less robust with the largest increase in $D_{1\%}$, while SFO plans showed more robustness with lowest increase in $D_{1\%}$. However, by applying robust optimization to IMRT plans (RB-IMRT), the worst case increase was reduced. In comparison to nominal plans, the highest worst case increase in the value of $D_{1\%}$ for brainstem, chiasm, spinal cord, optic nerves, and temporal lobes were 28.59%, 41.27%, 30.11%, 41%, and 14% for IMRT plan and, respectively, 17.65%, 20.76%, 21%, 24%, and 7.4% for SFO plan. The RB-IMRT plans resulted in more robust plans in comparison to the IMRT plans: with 24.6%, 28%, 25%, 26%, 8% increase respectively for brainstem, chiasm, spinal cord, optic nerves, and temporal lobes compared to the nominal RB-IMRT plans. In terms of absolute dose, the worst case analysis of different plans showed that robustness of HB-MFO plans was the best when compared to the competing nominal plans. Compared to the nominal doses, the worst case maximum in the mean dose delivered to cochlea was higher ($+27.1\%$ right; $+54.2\%$ left) for MFO plan and lower ($+8.3\%$ right; $+32.7\%$ left) for SFO plan. In terms of absolute dose, the HB-MFO plans resulted in the safest values.

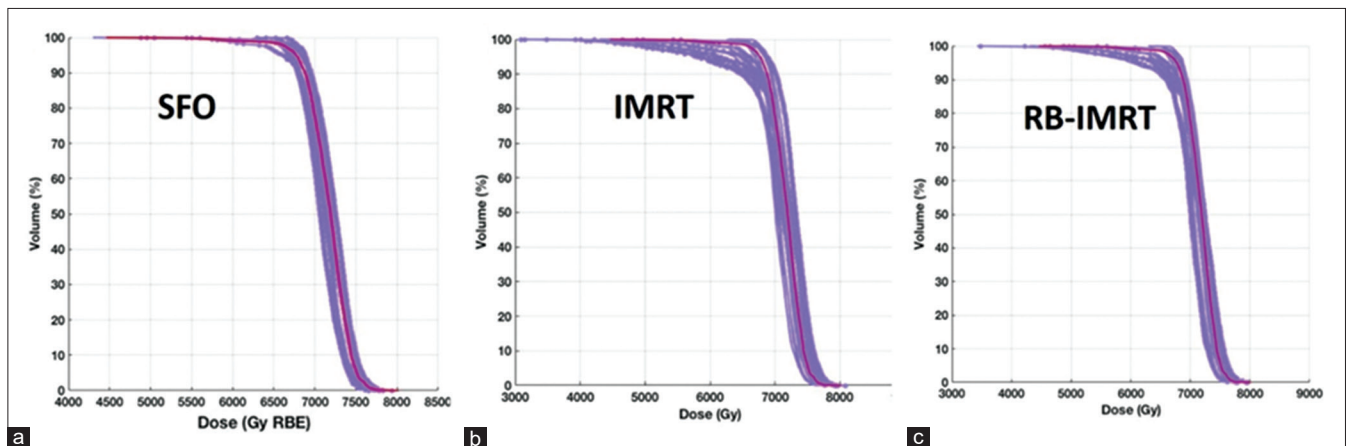


Figure 2: The nominal (red) and perturbed (blue) DVHs of a representative CTV-HR, resulted from the no-error and error introduced plans of SFO (a), IMRT (b) and RB-IMRT (c)

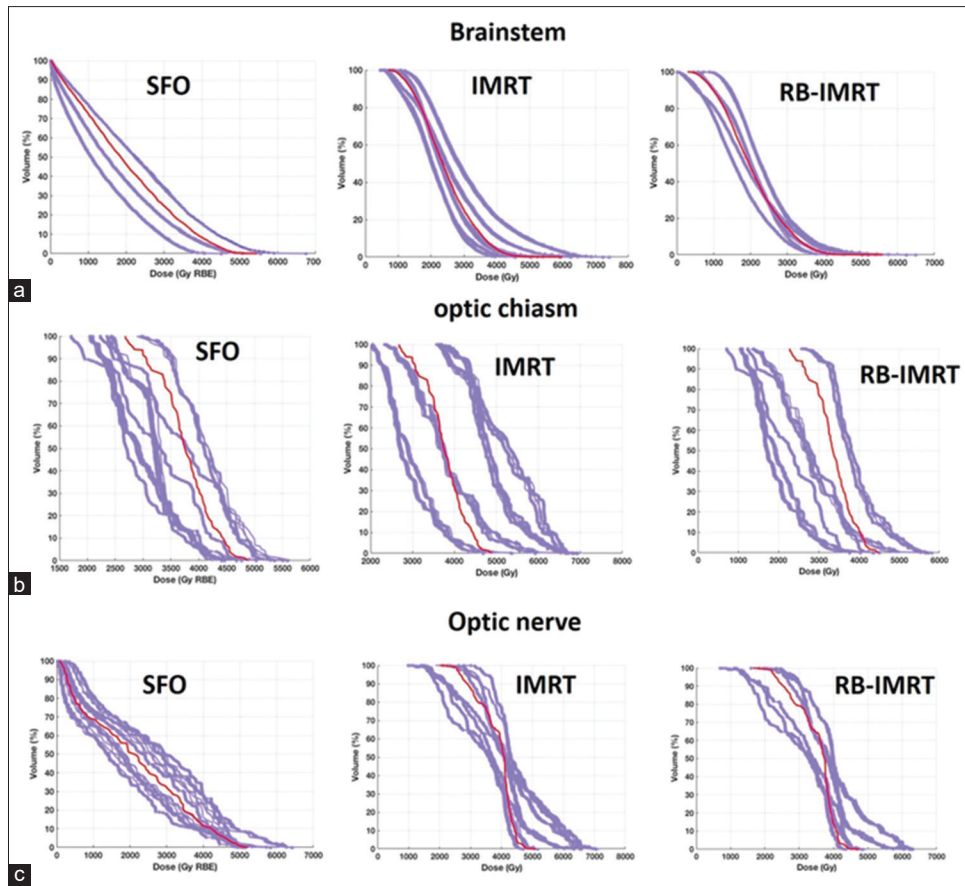


Figure 3: The nominal (red) and perturbed (blue) DVHs for select neurological OARs; brainstem (a), optic chiasm (b), and optic nerves (c), of the representative patient in three planning techniques (SFO, IMRT and RB-IMRT)

Table 4: The nominal maximum dose $D_{1\%}$ to various serial organs and mean dose D_{mean} to cochlea from the competing treatment plans and their worst case increase $D_{1\%}$ and D_{mean} . Units are Gy RBE for proton and Gy for photon plans

Structure	Indices	Techniques				
		SFO	MFO	HB-MFO	IMRT	RB-IMRT
Brain stem	NM- $D_{1\%}$	53.64±6.74	53.68±2.84	50.38±2.32	52.71±3.08	51.61±2.08
	WI- $D_{1\%}$	63.11±3.64	66.97±2.82	63.55±2.33	67.78±3.14	64.32±2.14
Chiasm	NM- $D_{1\%}$	52.84±1.72	52.81±1.38	50.09±1.81	50.10±3.65	50.10±1.80
	WI- $D_{1\%}$	63.81±3.38	66.20±2.92	63.62±2.40	70.78±4.32	64.12±3.10
Spinal cord	NM- $D_{1\%}$	46.65±3.00	47.02±3.70	44.55±2.30	45.52±3.70	45.10±3.10
	WI- $D_{1\%}$	59.20±2.46	62.87±1.32	58.69±2.30	65.14±2.52	60.10±1.84
RT-optic nerve	NM- $D_{1\%}$	58.14±8.21	54.92±8.50	52.35±2.32	53.09±6.31	52.01±3.30
	WI- $D_{1\%}$	66.59±3.34	67.17±5.94	65.60±2.04	69.53±1.62	66.32±3.52
LT-optic nerve	NM- $D_{1\%}$	51.22±2.18	51.40±3.70	49.50±1.10	49.15±2.90	50.71±3.10
	WI- $D_{1\%}$	63.48±5.20	64.83±1.69	63.20±1.76	69.32±3.03	64.10±1.89
RT-temporal lobe	NM- $D_{1\%}$	62.88±4.71	61.67±3.43	57.26±3.53	62.56±3.85	61.54±2.81
	WI- $D_{1\%}$	67.54±2.80	68.77±3.14	65.76±3.58	70.06±4.18	67.14±2.90
LT-temporal lobe	NM- $D_{1\%}$	63.49±3.93	62.53±5.86	57.39±4.44	63.93±4.40	62.13±3.30
	WI- $D_{1\%}$	68.03±2.72	68.84±4.26	65.60±3.74	71.47±4.39	66.60±3.39
RT-cochlea	NM- D_{mean}	36.63±8.19	34.47±7.25	27.45±3.08	37.27±8.34	33.12±4.89
	WI- D_{mean}	39.66±10.35	41.76±11.45	35.06±11.12	44.69±8.24	40.89±5.32
LT cochlea	NM- D_{mean}	31.77±17.3	30.97±17.40	28.84±18.8	34.74±15.10	32.12±14.35
	WI- D_{mean}	42.16±5.23	47.74±8.39	41.40±4.43	48.68±5.20	45.32±6.20

SFO: Single field uniform optimization, MFO: Multi field optimization, HB-MFO: Hybrid-multi field optimization, IMRT: Intensity modulated radiotherapy, RB-IMRT: Robustly optimized-intensity modulated radiotherapy, NM-D: Nominal maximum dose, WI-D: Worst case increase dose

Integral dose

Figure 4 shows the ID to normal tissue and few select OARs in both proton and photon plans. All three proton plans returned comparable IDs (Gy kg) to normal tissue with mean (\pm SD) of 16.7 ± 4.4 Gy kg in SFO, 14.6 ± 3.4 Gy kg in MFO and 12.9 ± 3.0 Gy kg in HB-MFO. As expected, almost two-fold increase in ID of normal tissue was observed in IMRT with mean (\pm SD) of 31.9 ± 6.6 Gy kg. In case of other OARs, comparable IDs were observed from all three proton plans. The absolute increase in the ID to OARs for IMRT plans is relatively lower: Compared to the best proton plan, a 60%–100% increment of ID was observed in IMRT plan.

DISCUSSIONS

Chordomas are difficult to manage because of the complex anatomy and its proximity to sensitive OARs with relevant physiological functions. Complete surgical resection is rarely accomplished due to its proximity to critical structures. Hence, historically, PBT has been considered the gold standard due to Bragg peak characteristic (i.e., delivering virtually no dose beyond the target). Several authors have reported excellent local control with limited high-grade toxicity.^[4,7,8] Most of these patients were treated with double scattering (DS) technique,^[4,8] which inherently produces dose spillage toward the proximal end of the target and hence, less conformal dose distribution. PBS has the potential to improve dose conformation around the target thereby reducing the dose to proximal OARs.^[11] At the same time, radiotherapy with photons also did improve significantly in the past years, with intensity-modulated techniques with static fields (IMRT) and arcs (VMAT). As a consequence, in our point of view, new comparative investigation between different proton planning techniques and photon IMRT in skull-based chordomas are timely.

Our study shows how the dosimetric outcome of proton plans for complex and challenging chordomas is highly dependent on the planning approach. In nominal scenarios, target coverage ($D_{98\%}$ and $D_{95\%}$) was compromised in all plans in order to respect the maximum dose ($D_{1\%}$) to surrounding serial OARs. The maximum dose ($D_{1\%}$) to all serial OARs was comparable among all plans and was within the clinically acceptable limit. The target coverage ($D_{95\%}$) of 62.32 to 66.70 Gy RBE, observed in different planning approaches in our study, is coherent with the values reported by Liu *et al.*^[22] In a dosimetric study of 10 patients with base of skull chordomas,

planned with 66 to 70 Gy RBE using IMPT, Liu *et al.*^[22] reported $D_{95\%}$ to CTV of 63.3 Gy RBE for conventional optimization to PTV and 64.8 Gy RBE for robust optimization to CTV. Among the 5 planning techniques investigated by this study, the new planning approach - HB-MFO - resulted in a better target coverage and sparing of OARs. In comparison to other proton and photon plans, HB-MFO delivered 2-7.5% higher dose (both $D_{98\%}$ and $D_{95\%}$) to target (CTV-HR) and lower $D_{1\%}$ of 4.4%–6.1% (brainstem), 0%–5.2% (chiasm), 2.1%–5.2% (spinal cord), 1.4%–9.9% (optic nerve), 7.2%–10.23% (temporal lobe) respectively.

Treatment planning and delivery in proton PBS technique are susceptible to range and set-up uncertainties: their impact on dosimetric outcomes depends on many factors, including the clinical site, beam angle, number of beams, treatment planning, and delivery methods. Different approaches are adopted to mitigate such uncertainties. Selection of appropriate beam directions, isotropic PTV-based optimization, beam-specific margin-based optimization and more recently CTV-based robust optimization incorporating both set-up and range uncertainties, are the commonly adopted approaches to mitigate uncertainties. Afterward, it is necessary to verify the plan quality for all uncertainty scenarios in order to meet clinical goals. That is why robustness evaluation is considered as an integral component of decision making in proton treatment plan, and should also be considered important in IMRT plans. While SFO is considered to be robust, PTV-based MFO strategy is reported as ineffective,^[23] due to the sensitivity of highly heterogeneous dose distributions from each field to set-up and range uncertainties. Therefore, instead of PTV based MFO, we adopted robust optimization based on CTV, taking into account both set-up and range uncertainty in MFO. We also evaluateies HB-MFO, which is the current standard in Trento Proton Therapy Center. The main reason for choosing HB-MFO is the significant time reduction for dose optimization, especially when a MC dose calculation code is needed (i.e., HB-MFO optimization requires to calculate and optimize 3 different scenarios compared to the 21 scenarios in the full-MFO). In comparison to nominal case scenario, robust evaluation of different proton plans showed that worst case decrease in target coverage was comparable for MFO and HB-MFO and was lower in SFO.

In the current practice of photon IMRT, uncertainties are usually dealt by providing margins around the CTV and

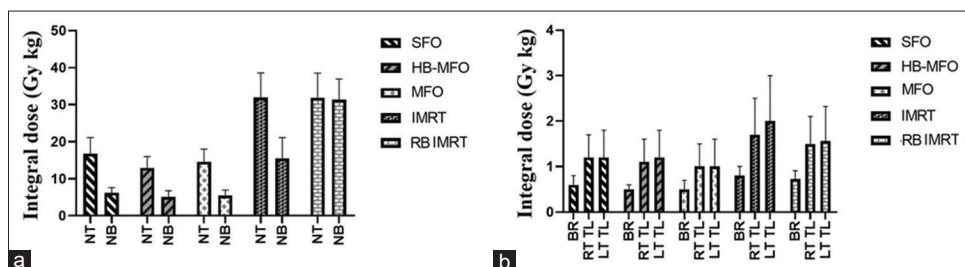


Figure 4: The integral dose to (a) Normal tissue, normal brain, (b) brain stem, right temporal lobe, left temporal lobe from both proton and photon plans

critical organs, thus creating PTV and PRV, as recommended by the International Commission on Radiation Units and Measurements (ICRU) report 83.^[24] Although CTV to PTV margin represented a significant step ahead in the inclusion of geometrical uncertainties in the planning procedures, it is a first approximation rather than a complete solution to the problem. An explicit inclusion of geometrical uncertainties in the optimization procedures for photons may provide a more complete approach to find the right balance between target coverage and OAR sparing. In agreement to other studies,^[25] we also found that even after assigning margins, variations arise in the delivered dose received by the tumor and OARs. We found a slightly lower robustness in both targets and OARs for IMRT, compared to the SFO, MFO and HB-MFO proton plans. On the contrary, the worst case scenario in robustly optimized IMRT plans resulted in a maximum of 6 to 7% CTV coverage improvement and a maximum 4% (brainstem), 13.3% (chiasm), 9.8% (spinal cord), and 14% (optic nerve) decrease in the $D_{1\%}$ of the serial OARs. This led us to state that robustly optimized IMRT plans are less sensitive to set-up uncertainties in comparison to not robustly optimized ones. Similar observations were reported by Miura *et al.*^[26] Their phantom based study in PTV, they showed that nonrobust volumetric-modulated arc therapy (VMAT), are less robust than robustly optimized CTV-based VMAT plans for set up uncertainties. Our study points out the need to consider robust optimization-based IMRT plans and also that robust evaluation should be performed before clinical selection of IMRT and proton plans. However, we have also found significant differences in the low dose areas between the IMRT and MFO techniques. The ID calculated for normal tissues was higher in IMRT plans, confirming the suitability of MFO proton plans over IMRT.

A message clearly emerging from our data, which we believe has to be shared with the scientific community, is that robustness evaluation metric showed significant differences, both in terms of target and OARs sparing, between the nominal plan approved by the clinician and the worst case scenarios. This is true both for photon and proton plans: ‘robustness metric’ is not a peculiarity of proton therapy. On the other hand, it is extremely important to define a benchmark for the worst scenarios, in order to understand what a safe variability is (i.e., a spinal cord $D_{1\%}$ of 65 Gy of a worst case scenario compared to 45 Gy of the nominal one: still safe or requires a plan re-optimization?). We believed that the use of standard IMRT as a benchmark (because of its level of diffusion) for proton plans could be a reasonable approach, but also using robust analysis results from patients already treated with protons (i.e., with follow-up data on toxicity and tumor control) could be an interesting solution, as proposed by Malyapa *et al.*^[27] Another important consideration must be made when robustness is applied to OARs and not only to the target. The OARs constraints, reported in the QUANTEC papers,^[28] are all based on the nominal DVH and no robust analysis of that constraints was taken into account. Some limitations of

our study must be carefully considered: (1) only five clinical cases are included, (2) different intensity modulated photon techniques (i.e., VMAT, Tomotherapy, Cyberknife, etc.) can give different results, and (3) even with the same IMRT technique, we can use other optimization algorithms/cost functions which can have a different impact on plan robustness. Further investigation on large patient datasets of various clinical sites will help in drawing a more concrete conclusion.

CONCLUSION

Based on the five cases presented in the current study, all proton planning techniques (SFO, MFO and HB-MFO) were robust both for target coverage and OARs sparing. Standard IMRT plans were less robust than proton plans in regards to high doses to neurological OARs. However, robust optimization applied to IMRT resulted in improved robustness in both target coverage and high doses to OARs. Robustness evaluation may be considered as a part of plan evaluation procedure even in IMRT.

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Conflicts of interest

There are no conflicts of interest.

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