Dosimetric comparison of five different techniques for craniospinal irradiation across 15 European centers: Analysis on behalf of the SIOP-E-BTG (radiotherapy working group)

Enrica Seravalli (1), M. Bosman (1), Yasmin Lassen-Ramshad (2), Anne Vestergaard (2), Foppe Oldenburger (3), Jorrit Visser (3), Efi Koutsouveli (4), Chryssa Paraskevopoulou (4), Gail Horan (5), Thankamma Ajithkumar (5), Beate Timmermann (6), Carolina Fuentes (6), Gillian Whitfield (7), Thomas Marchant (7), Laetitia Padovani (8), Eloise. Garnier (8), Lorenza Gandola (9), Silvia Meroni (9), Bianca Hoeben (10), Martijn Kusters (10), Claire Alapetite (11), S. Losa (11), F. Goudjil (11), Henriette Magelssen (12), M. Evensen (12), Frank Saran (13), Gregory Smyth (13), Barbara Rombi (14), Roberto Righetto (14), Rolf-Dieter Kortmann (15), Geert O. Janssens (1)

(1) Department of Radiation Oncology, University Medical Centre Utrecht and Princess Maxima Centre for Pediatric Oncology, Utrecht, The Netherlands.
(2) Dept. of Oncology and Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark
(3) Dept. of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands
(4) Dept. of Radiation Oncology, Hygeia Hospital, Athens, Greece
(5) Dept. of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
(6) Clinic for Particle Therapy, West German Protontherapy Center Essen, University Hospital Essen, Germany
(7) The Christie NHS Foundation Trust, Manchester, UK

(8) Dept. of Radiotherapy, Centre Hospitalier Universitaire de La Timone, Marseille, France
(9) Pediatric Radiotherapy Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
(10) Dept. of Radiation Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
(11) Department of Radiation Oncology, Institut Curie and Centre de protontherapie, Paris & Orsay, France
(12) Dept. of Radiation Oncology, Norwegian Radium Hospital, University of Oslo, Oslo, Norway
(13) The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom
(14) Protontherapy Center, Azienda Provinciale per i Servizi Sanitari APSS, Trento, Italy
(15) Dept. of Radiation Therapy, University Hospital Leipzig, Leipzig, Germany

Corresponding author:

Enrica Seravalli (PhD), Department of Radiation Oncology, University Medical Centre Utrecht and Princess Maxima Centre for Pediatric Oncology, Postbox, 3508 GA Utrecht, The Netherlands.

Phone: 00-31-88-7560496 E-mail: E.Seravalli@umcutrecht.nl

Short title : CSI by 3D-CRT, IMRT, VMAT, TomoTherapy® or PBS

Number of pages: 40

Word count: 3027

Tables: 4 plus 1 as supplementary material

Figures: 3 plus 1 as supplementary material

CONFLICT OF INTEREST NOTIFICATION

Actual or potential conflicts of interest for this study do not exist.

ABSTRACT

Purpose:

Conventional techniques (3D-CRT) for craniospinal irradiation (CSI) are still widely used. Modern techniques (IMRT, VMAT, TomoTherapy®, proton pencil beam scanning [PBS]) are applied in a limited number of centers.

For a 14-year old patient, we aimed to compare dose distributions of five CSI techniques applied across Europe and generated according to the participating institute protocols, therefore representing daily practice.

Material & Methods:

A multicenter (n=15) dosimetric analysis of five different techniques for CSI (3D-CRT, IMRT, VMAT, TomoTherapy®, PBS; 3 centers per technique) was performed using the same patient data, set of delineations, and dose prescription (36.0/1.8Gy). Different treatment plans were optimized based on the same planning target volume margin. All participating institutes returned their best treatment plan applicable in clinic.

Results:

The modern radiotherapy techniques investigated resulted in superior conformity/homogeneity-indices (CI/HI), particularly in the spinal part of the target (CI: 3D-CRT:0.3 vs. modern:0.6; HI: 3D-CRT:0.2 vs. modern:0.1), and demonstrated a decreased dose to the thyroid, heart, esophagus, and pancreas. Dose reductions of >10.0Gy were observed with PBS compared to modern photon techniques for parotid glands, thyroid, and pancreas. Per technique, a wide range in dosimetry among centers using the same technique was observed (e.g. thyroid mean dose: VMAT: 5.6–24.6Gy; PBS: 0.3–10.1Gy).

Conclusions:

The investigated modern radiotherapy techniques demonstrate superior dosimetric results compared to 3D-CRT. The lowest mean dose for organs at risk is obtained with proton therapy. However, for a large number of organs ranges in mean doses were wide and

overlapping between techniques making it difficult to recommend one radiotherapy technique over another.

Funding

None declared

KEYWORDS

Craniospinal irradiation, conventional technique, 3D-CRT, VMAT, IMRT, TomoTherapy®, proton therapy, dose comparison

PRESENTATIONS

This study was presented at the ESTRO 36 meeting, Vienna, Austria, May 6-9, 2017.

INTRODUCTION

Craniospinal irradiation (CSI) is indicated for medulloblastoma and some rarer tumors with signs of leptomeningeal spread, particularly germ-cell tumors, atypical teratoid rhabdoid tumors, and ependymomas [1-8].

The technique most commonly used for treating the craniospinal axis is a combination of two lateral opposed photons beams for the brain, matched to one or more posterior photon fields to treat the spine [9,10]. This approach results in dose inhomogeneity, especially at the beam junction(s), and a significant dose anterior to the spinal target volume. Over the last decade, other techniques for CSI have been investigated in order to decrease the dose to the organs outside the target volume, in particular the thyroid, heart, and intestines [11-15]. Intensity-Modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT), and TomoTherapy® are highly conformal techniques which can reduce the dose to the structures anterior to the vertebrae at the expense of a larger volume of low-dose irradiation to the entire body. Due to the steep dose gradient, both electron and proton beam radiation provide substantial sparing of non-target tissues anterior to the spinal target volume compared to photons [16,17].

In clinical practice, the reason for using more conformal techniques is better sparing of healthy tissue. However, the vast majority of late effects reported after CSI in childhood arise from irradiation of the target volume [18-21]. Dose and age influence toxicity outcome and are the justification for dose reduction, altered fractionation regimens, a combination with systemic agents or target volume adaptations [22-26]. Further decrease of late toxicity, e.g. second malignancies outside the target volume, primary hypothyroidism, cardiovascular events, restrictive lung disease, and metabolic syndrome might be obtained with modern radiotherapy techniques that lower the dose to the structures anterior to the vertebrae without compromising the target coverage [21,27-32].

The lack of exit dose and high conformity observed with protons are potential reasons for referring patients with a CSI indication to proton therapy centers. However, when referring

for proton therapy it is important to balance other factors, such as treatment delay, accessibility, associated financial issues, social disruption of the family, and secondary malignancy estimation.

The question we tried to answer in this work was how radiation type and technique influences target dose coverage and OAR dose burden, and how these variables vary when such techniques are executed by different institutions.

In this study we compare dose distributions of five CSI techniques currently applied across Europe, generated for a single patient and according to the participating institute protocols, therefore representing daily practice.

To the authors' knowledge, this is the first time a CSI dose distribution comparison has been performed using the same patient data and with three different institutes plan each of the considered delivery techniques.

METHODS & MATERIALS

A CT scan from a 14-year-old boy, previously irradiated for high-risk medulloblastoma, was selected. Approval for the study was obtained from the University Medical Center Utrecht, Research Ethics Committee.

An individual head-neck support with five-point fixation mask (Civco Medical Solutions, Kalona, Iowa, USA), vacuum mattress (BlueBag^{TM} Vacuum Cushion, Elekta, Stockholm, Sweden), and a customized knee-feet fixation (MacroMedics BV, Waddinxveen, The Netherlands) were used to scan (slice thickness 3 mm) the patient in a supine position for radiotherapy.

Contouring of the clinical target volume (CTV) and organs at risk (OAR) was performed at one center (Utrecht, The Netherlands). The cranial part of the CTV comprised the entire brain, cranial nerves, and meninges. The spinal part of the CTV contained the spinal canal as observed on CT scan including the cerebrospinal fluid extension to the spinal ganglia. The inferior limit of the spinal CTV was defined by a co-registered MRI at the caudal extent of the thecal sac.

The planning target volume (PTV) consisted of an uniform expansion around the CTV of 5 mm for the brain (PTV_{brain}) and the spinal levels C1-L2 (PTV_{spine}), and of 8 mm for the levels L3-S3 (PTV_{spine}). PTV_{total} is defined as the combination of PTV_{brain} and PTV_{spine}. Outlined OARs included: scalp, left/right lenses, left/right parotid and submandibular glands, thyroid, larynx and proximal esophagus, esophagus, heart, left/right lungs, intestines and stomach, pancreas, and left/right kidneys. The total normal tissue volume (TNTV) corresponds to the external contour of the body, imaged on the CT scan, minus PTV_{total}.

Treatment planning

The radiotherapy department of the University Medical Center Utrecht, The Netherlands, sent the CT-scan with contours to fourteen additional SIOP-E-linked institutes participating in this study. Each center used either 3D-CRT, IMRT, VMAT, TomoTherapy® (in the

following Tomotherapy), or PBS for CSI, and three centers per technique were included. Selection of participating centers was based on participation in the radiotherapy working group meeting of the SIOP-E-Brain Tumor Group and the availability to generate a respective treatment plan for CSI. Three institutes per technique were randomly identified.

All participating institutes were asked to return the best treatment plan, applicable in daily practice, for a dose prescription of 36.0 Gy in 20 fractions of 1.8 Gy, and meeting the following criteria: (1) high weighing for PTV_{total} coverage (at least 95% of PTV_{total} should receive 95% of the prescribed dose), and (2) maximal sparing of the OARs.

An overview of the major characteristics per technique and per center is listed in Table 1. An overview of the constraints used by the centers is given in Table S1.

In order to quantify inter-patient dosimetric differences on organs at risk five patients with indication for CSI, previously irradiated at the radiotherapy department of the University Medical Center Utrecht, were re-planned using VMAT by the same planner for a dose-prescription of 36.0 Gy in 20 fractions of 1.8 Gy.

Table 1. Overview of the treatment planning geometry per technique, and per center.

	Center	3D-CRT	IMRT	VMAT	Tomotherapy	PBS
TPS	1	Eclipse	Pinnacle	Monaco	Tomotherapy	Raystation
	2	Pinnacle	Pinnacle	Eclipse	Tomotherapy Tomotherapy	Eclipse
	3	Oncentra Masterplan	Oncentra	Monaco		Raystation
Dose algorithm	1	AAA,	Collapsed cone	Monte Carlo	Convolution-superposition	Pencil beam
	2	Adaptive Convolve	Adaptive Convolve	AAA	Collapsed cone	Pencil beam
	3	Collapsed Cone	Collapsed cone	Monte Carlo	Collapsed cone	Pencil beam
Dose grid size (mm)	1	2	4	3	2.15	2
	2	2.5	3	2.5	2.15	2
	3	3	2	3	2.54	2
Energy (MV)	1	6, 15	6	6	6	180 MeV-100 MeV
	2	6	6	6	6	180 MeV-100 MeV
	3	6, 15	6	6	6	180 MeV – 70 MeV
Technique characteristics Brain	1	-	Forward planned	Full arc	Full arc	Spot size 3 mm, range shifter thickness 75 mm, all MUs delivered with range shifter, airgap 300mm, robust optimization
	2	Forward planned	Forward planned	Full arc	Full arc	Spot size depends on depth, range shifter 75mm, all MU's delivered with range shifter, airgap 20mm, robust optimization
	3	-	2 IMRT beams	2 partial arcs	Full arc	Spot size 3 mm, range shifter thickness 40 mm, the percentage of MU's delivered with range shifter depends on beam, airgap 300mm, single field optimization
Spine	1	-	Posterior fields	2 posterior partial arcs	Full arc	Same as for brain
	2	At extended ssd	Posterior fields inverse opt	2 partial arcs	Full arc	Same as for brain
	3	-	5 IMRT beams	3 partial arcs	Full arc	Same as for brain
Number of isocenters	1	3	3	3	1	3
	2	2	3	3	1	3
	3	3	3	3	1	3
Isocenter location	1	mid brain, thoracic/lumbar spine	mid brain, thoracic/lumbar spine	mid brain, thoracic/lumbar spine	-	C1, thoracic/lumbar spine
	2	mid brain, thoracic spine	mid brain, thoracic/lumbar spine	mid brain, thoracic/lumbar spine		mid brain, thoracic/lumbar spine
	3	mid brain, thoracic/lumbar spine	mid brain, thoracic/lumbar spine	mid brain, thoracic/lumbar spine		mid brain, thoracic/lumbar spine
Beam(s) gantry angle* (°)	1	Brain: 85, 272 Spine: 180	Brain: 90, 270 Spine: 120, 145, 180, 215, 240	Brain: 180.1-179.9 Spine: 180-240 and 100-180	-	Brain: 30, 330 Spine: 0
	2	Brain: 90, 270 Spine: 180	Brain: 90, 270 Spine: 135, 180, 225	Brain and spine: 180.1 – 179.9 Avoidance sectors: thoracic spine: 245-320, 50-115, lumbar spine: 230-300, 67-130 Brain: 180-130, 50/130		Brain:30, 330 Spine : 180
	3	Brain: 85, 270 Spine: 180	Brain: 90, 270 Spine: 120, 150, 180, 210, 240	Thoracic spine: 180-90, 90-90, 300-120 Lumbar spine: 180-90, 90-90, 300-120		Brain: 180, 90 couch - 15, 270 couch 15, Spine: 180
Number of junctions	1	3	2	2	-	2
	2	3	2	2		2
	3	2	2	2		2
Length of junction in CC direction (cm)	1	6	6	8	-	10
	2	1.6	4	3		8
	3	1.5	3	3		8

Abbreviations: TPS: Treatment Planning System; CC: Cranio Caudal direction; SSD: Source-to-Skin-Distance

* For VMAT the start/stop gantry angle of the arc is indicated

Plan evaluation

Radiotherapy treatment plans were compared per technique and each specific technique also between centers. Dose-volume histograms were evaluated for the PTVs (PTV_{total}, PTV_{brain} and PTV_{spine}) and the OARs. Conformity index (CI) and homogeneity index (HI) were calculated by using the van 't Riet formula [33] (CI: range 0-1, with 1 being highly-conformal) and Kataria formula [34] (HI: range 0-1, with 1 being highly heterogeneous):

$$\mathrm{CI} = \frac{\left(\mathrm{V}_{95\%}^{\mathrm{PTV}}\right)^2}{\mathrm{V}^{\mathrm{PTV}} \times \mathrm{V}_{95\%}}$$

$$HI = \frac{D_{2\%}^{PTV} - D_{98\%}^{PTV}}{D_{mean}^{PTV}}$$

In the formula: $V_{95\%}$ represents the volume receiving at least 95% of the prescribed dose; $D_{x\%}$ the dose received by x% of the volume of the PTV.

For the TNTV the percentage of volume receiving at least 1.0, 2.0, 5.0, 34.2 and 36.0 Gy was calculated. The median and range (minimum/maximum) of each of the dosimetric parameters were computed for each technique.

Superiority of the different techniques was assessed based on the highest conformity (highest CI) and homogeneity (lowest HI) for the PTV, in combination with the lowest mean dose to the OARs.

For the purpose of this study, a difference between techniques is considered of "potential clinical significance" if a mean dose difference ≥5.0 Gy is observed for the OARs. This threshold is chosen based on a consensus between the participating institutes.

RESULTS

Figure 1 represents the dose distribution in a sagittal plane for a 14-year old boy, receiving 36.0 Gy by the five different radiotherapy techniques considered in this work.

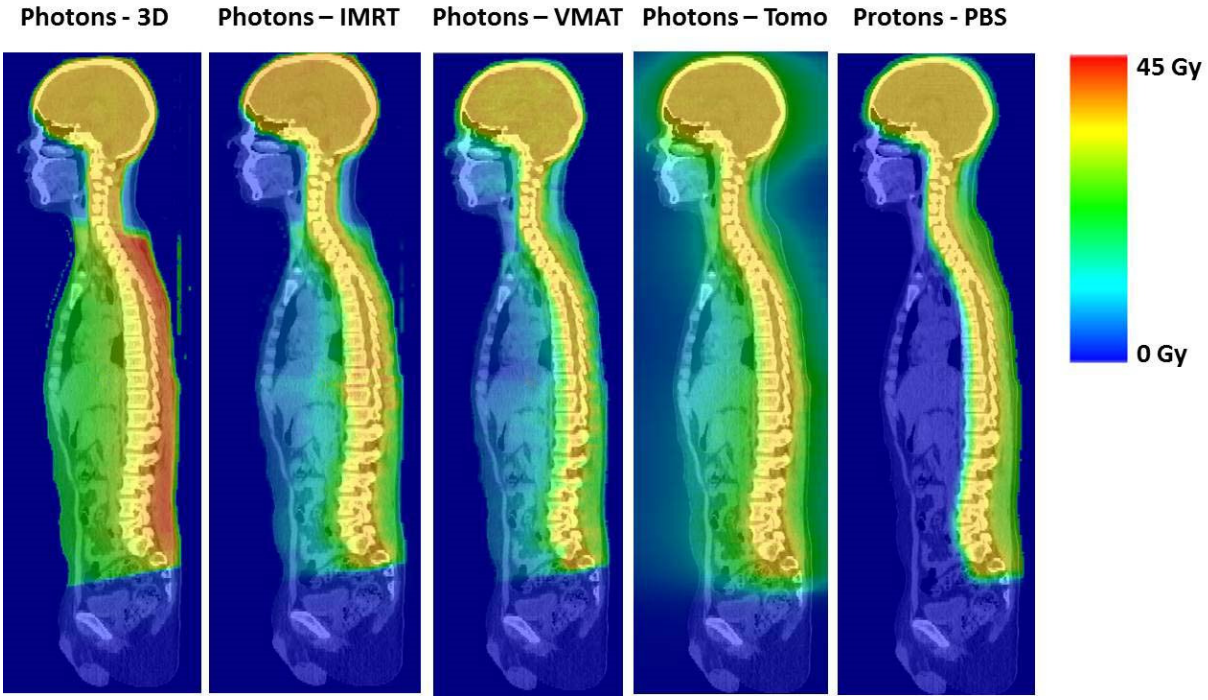

Figure 1. Craniospinal axis dose distribution with photons (3D-CRT, IMRT, VMAT, Tomotherapy) and protons. Only one out of three generated plans per technique is depicted.

Conformity and homogeneity

The median CI for the PTV_{total} of all modern radiotherapy techniques was superior compared to 3D-CRT, and this was attributable to the spinal part of the target volume (Table 2). The median HI for PTV_{total} was similar for all techniques when considering the range of data per technique, however better median HI values for PTV_{spine} were observed with modern radiotherapy techniques (Table 2).

In particular for the 3D-CRT technique, hot spots within the PTV_{spine} (V107%: 10.6-27.1%) and absolute doses above 40.0 Gy (111 %) were observed (Table 2).

The largest variation between centers using the same technique for the CI of the PTV_{brain} was found for IMRT (0.8-1.0) and PBS (0.7-0.9). For the CI of the PTV_{spine} , largest

variation was observed for VMAT (0.6-0.8), Tomotherapy (0.5-0.7) and PBS (0.5-0.7). PBS dose distributions showed the widest range in D2% (PTV_{brain}: 36.4-40.0 Gy; PTV_{spine}: 36.4-39.6) while VMAT dose distributions in D98% (PTV_{brain}: 33.7-35.5 Gy; PTV_{spine}: 33.7-35.2 Gy) (Figure 2and Table 2).

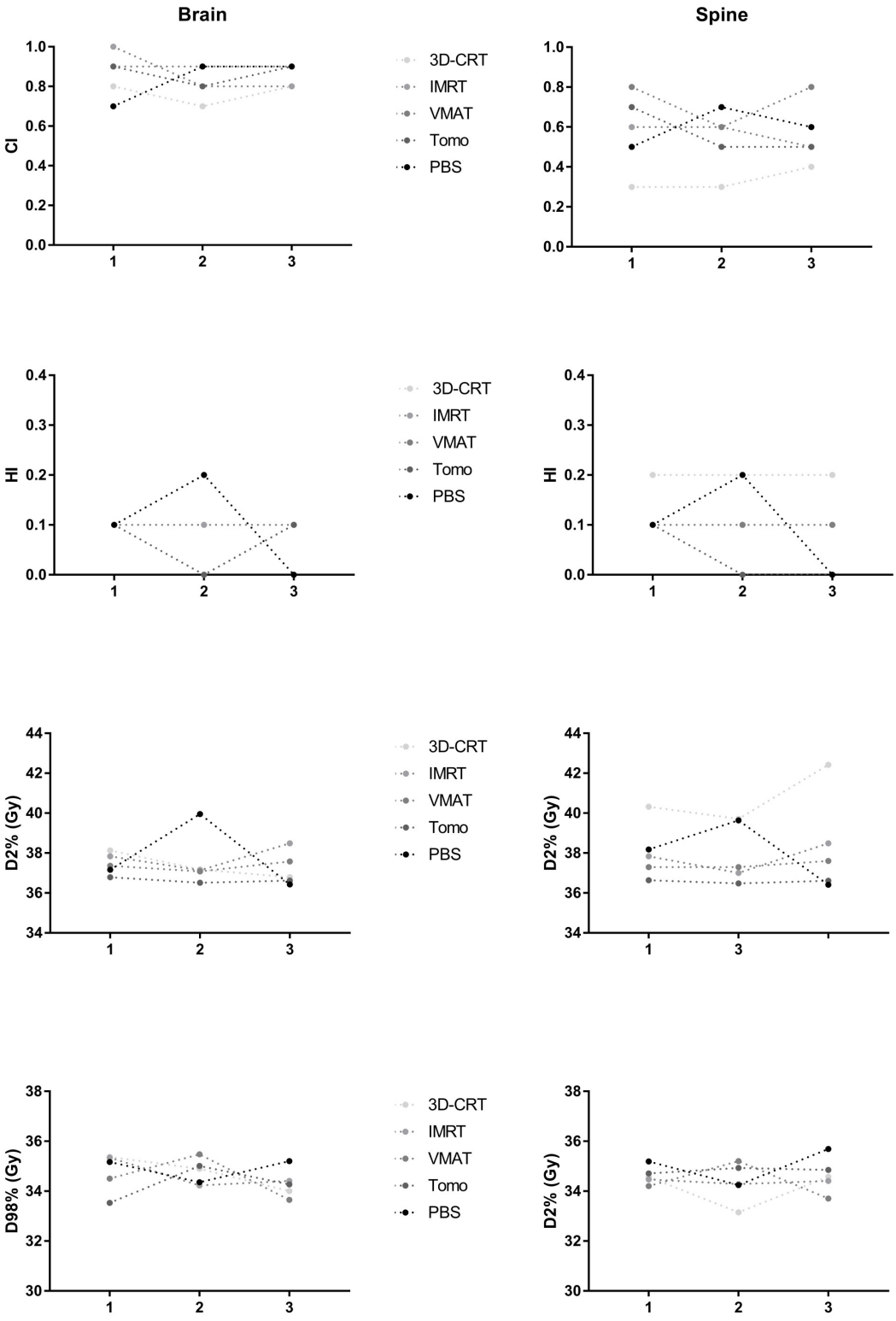

Figure 2 CI, HI, D2% and D98% of the PTV_{brain} and PTV_{spine} per center per technique

232

233 **Normal tissue sparing**

234 Compared with 3D-CRT, a decrease in the mean dose to the thyroid by more than 10.0 Gy
235 (28.5 Gy vs. 15.1* Gy) was observed for all modern photon radiotherapy techniques, while a
236 decrease between 5.0 and 10.0 Gy for the mean dose of both parotid glands (20.5 Gy vs
237 14.9* Gy), heart (13.4 Gy vs. 8.1* Gy), esophagus (29.9 Gy vs. 20.7* Gy) and pancreas
238 (17.1 Gy vs. 11.5* Gy) was seen (Figure 3, Table 3).

239 With respect to modern photon techniques, PBS further reduced the mean dose to the OARs
240 by more than 10.0 Gy for the average of both parotid glands (14.9* Gy vs. 4.0 Gy), thyroid
241 (15.1* Gy vs. 0.8 Gy), esophagus (20.7* Gy vs. 2.3 Gy) and pancreas (11.5* Gy vs. 0.0 Gy)
242 while mean dose benefits between 5.0 to10.0 Gy were observed for the lenses (9.2* Gy vs.
243 1.8 Gy), submandibular glands (7.9* Gy vs. 1.4 Gy), larynx and proximal esophagus (11.1*
244 Gy vs. 2.3 Gy), heart (8.1* Gy vs. 0.0 Gy), lungs (8.3* Gy vs. 2.2 Gy), and intestines (9.6*
245 Gy vs. 0.4 Gy) (Figure 3, Table 3).

246 When comparing one specific radiotherapy technique among the three participating centers,
247 a wide range in mean doses delivered to the OARs was found (Table 3). Ranges of >10.0 Gy
248 were observed for the lenses (Tomotherapy), thyroid (VMAT, Tomotherapy), larynx +
249 proximal esophagus (3D-CRT, VMAT, Tomotherapy, PBS), and esophagus (VMAT,
250 Tomotherapy). Differences larger than 10Gy for D1cc between centers applying the same
251 technique were even more frequent (Table 4). D_{mean} ranges between 5.0 to 10.0 Gy were
252 seen for the lenses (3D-CRT, VMAT, PBS), parotid and submandibular glands (3D-CRT,
253 VMAT, PBS), thyroid (IMRT, PBS), heart (VMAT), intestines-stomach, pancreas and
254 esophagus (VMAT, Tomotherapy), and kidneys (PBS). The range in mean doses for OARs of
255 the spine was the narrowest for 3D-CRT.

* Average of the Dmean median value of the three modern photon techniques

For all photon techniques, 3D-CRT provided the smallest V1Gy, V2Gy and V5Gy of the TNTV but the highest V34.2Gy and V36Gy. Overlap in TNTV dose was observed for the three modern photon techniques. The lowest TNTV dose was observed with PBS (Table 2).

The largest inter-patient difference (maximum minus minimum value) found in D_{mean} for all OARs, considered in the manuscript, is 3 Gy (data not shown).

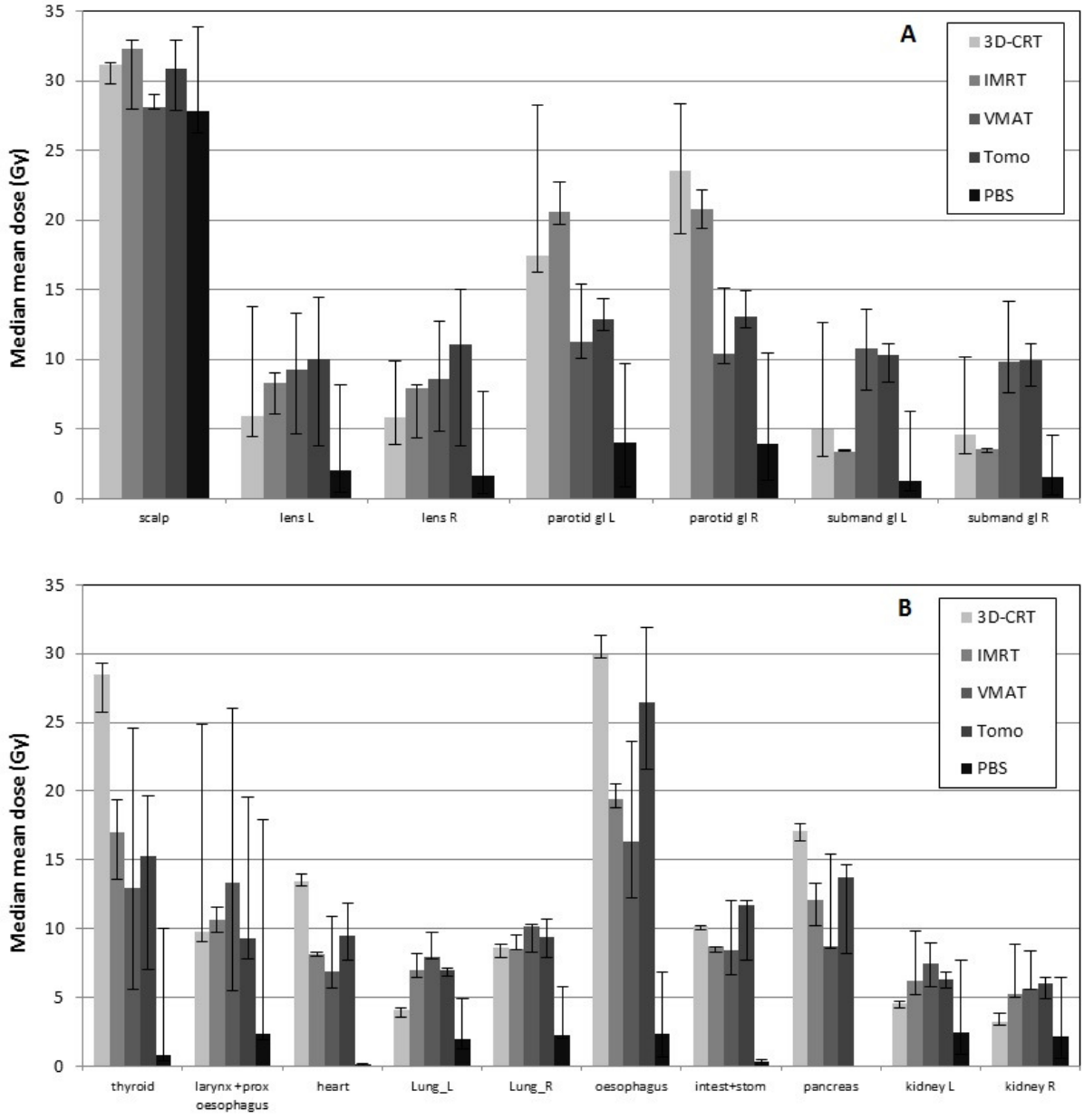

Figure 3.
Median D_{mean} (Gy) for the organs at risk surrounding the brain (A) and the spine (B). Error bars show the range (min, max) per technique
[Tomo: Tomotherapy; PBS: proton pencil beam scanning].

Table 2. Dosimetric parameters for PTVs and total normal tissue volume per technique

	3D-CRT	IMRT	VMAT	Tomo	PBS
	Median [Range]	Median [Range]	Median [Range]	Median [Range]	Median [Range]
PTV total dosimetry					
V95% (%)	97.8 [97.7-99.7]	98.3 [97.0-99.7]	98.8 [96.2-100.0]	98.2 [96.8-99.7]	99.8 [98.4-99.9]
V107% (%)	5.5 [2.8-7.1]	0.0 [0.0-1.5]	0.0 [0.0-0.2]	0.0 [0.0-0.0]	0.1 [0.0-6.4]
Dmean (Gy)	36.4 [36.1-37.2]	36.7 [36.0-36.8]	35.9 [35.7-36.1]	35.9 [35.8-36.0]	36.0 [36.0-36.1]
D2% (Gy)	39.4 [38.8-40.5]	37.8 [37.1-38.4]	37.3 [37.1-37.6]	36.6 [36.5-36.8]	37.7 [36.4-39.8]
D98% (Gy)	34.1 [34.1-34.9]	34.3 [33.8-34.8]	34.4 [33.8-35.4]	34.3 [33.7-35.0]	35.2 [34.3-35.3]
CI	0.6 [0.5-0.6]	0.7 [0.6 -0.7]	0.9 [0.8-0.9]	0.8 [0.7-0.9]	0.8 [0.7-0.8]
HI	0.1 [0.1-0.2]	0.1 [0.08-0.1]	0.1 [0.0-0.1]	0.1 [0.04-0.1]	0.1 [0.03-0.2]
PTV brain dosimetry					
V95% (%)	99.1 [97.1-99.9]	98.3 [98.2-99.9]	99.2 [95.1-99.9]	98.1 [96.4-99.5]	99.7 [98.8-99.8]
V107% (%)	0.0 [0.0-0.0]	0.0 [0.0-1.7]	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.0 [0.0-7.4]
Dmean (Gy)	36.3 [35.6-37.2]	36.9 [36.0-37.0]	35.9 [35.6-36.1]	35.9 [35.8-36.0]	36.1 [36.0-36.1]
D2% (Gy)	37.2 [36.8-38.1]	37.8 [37.1-38.5]	37.4 [37.1-37.6]	36.6 [36.5-36.8]	37.2 [36.4-40.0]
D98% (Gy)	34.9 [34.0-35.4]	34.4 [34.2-35.3]	34.5 [33.7-35.5]	34.3 [33.5-35.0]	35.2 [34.4-35.2]
CI	0.8 [0.7-0.8]	0.8 [0.8-1.0]	0.9 [0.8-0.9]	0.9 [0.8-0.9]	0.9 [0.7-0.9]
HI	0.1 [0.06-0.1]	0.1 [0.07-0.1]	0.1 [0.0-0.1]	0.1 [0.0-0.1]	0.1 [0.0-0.2]
PTV spine dosimetry					
V95% (%)	99.3 [94.0-99.3]	98.2 [94.2-99.1]	99.7 [97.9-99.9]	99.5 [98.8-99.6]	99.8 [98.2-99.9]
V107% (%)	20.7 [10.6-27.1]	0.2 [0.0-0.4]	0.0 [0.0-0.3]	0.0 [0.0-0.0]	0.2 [0.0-3.7]
Dmean (Gy)	37.2 [36.5-37.5]	36.0 [35.9-36.2]	35.8 [35.8-36.2]	35.9 [35.8-35.9]	36.0 [35.9-36.3]
D2% (Gy)	40.3 [39.7-42.4]	37.8 [37.0-38.5]	37.3 [37.3-37.6]	36.6 [36.5-36.6]	38.2 [36.4-39.6]
D98% (Gy)	34.6 [33.2-34.6]	34.4 [34.3-34.5]	34.2 [33.7-35.2]	34.9 [34.7-34.9]	35.2 [34.2-35.7]
CI	0.3 [0.3-0.4]	0.6 [0.5-0.6]	0.8 [0.6-0.8]	0.5 [0.5-0.7]	0.6 [0.5-0.7]
HI	0.2 [0.1-0.2]	0.1 [0.08-0.1]	0.1 [0.06-0.1]	0.0 [0.0-0.1]	0.1 [0.0-0.2]
TNTV					
V1Gy (%)	52.6 [46.1-56.1]	66.1 [64.9-79.6]	70.2 [63.7-75.5]	69.5 [62.5-71.7]	15.4 [11.3-20.1]
V2Gy (%)	35.9 [33.-38.3]	57.2 [52.9-62.4]	62.2 [54.8-71.5]	60.1 [52.7-64.2]	14.1 [10.5-18.5]
V5Gy (%)	22.9 [22.2-23.4]	41.7 [38.9-48.0]	43.3 [38.6-48.7]	45.9 [37.4-49.7]	12.2 [9.1-16.1]
V34.2Gy (%)	5.1 [5.0-5.3]	3.4 [1.9-3.5]	0.7 [0.7-1.7]	1.7 [0.5-2.1]	1.3 [1.0-2.9]
V36Gy (%)	3.7 [3.2-3.7]	0.9 [0.8-1.6]	0.1 [0.1-0.5]	0.3 [0.01-0.3]	0.4 [0.2-0.8]

Vx% is the volume receiving at least x% of the prescribed dose
Dx% is the dose received by x% of the volume
VxGy is the volume receiving at least xGy of the prescribed dose
CI is the conformity index
HI is the homogeneity index

Table 3. D_{mean}(Gy) for organs at risk with individual techniques

Dmean OARs	3D-CRT	IMRT	VMAT	Tomo	PBS
	Median [Range]	Median [Range]	Median [Range]	Median [Range]	Median [Range]
Scalp (Gy)	31.2 [29.8-31.3]	32.3 [28.0-32.9]	28.1 [28.0-29.0]	30.9 [27.9-32.9]	27.8 [26.3-34.0]
Lens L (Gy)	5.9 *[4.5-13.8]*	8.3 [6.1-9.0]	9.3 *[4.6-13.3]*	10.1 **[3.8-14.5]**	2.0 *[0.5-8.2]*
Lens R (Gy)	5.8 *[3.9-9.9]*	8.0 [4.3-8.2]	8.6 *[4.8-12.7]*	11.1 **[3.8-15.0]**	1.7 *[0.4-7.7]*
Parotid gland L (Gy)	23.5 *[19.0-28.4]*	20.8 [19.4-22.2]	10.4 *[9.7-15.1]*	13.1 [12.2-15.0]	4.0 [1.3-10.5]
Parotid gland R (Gy)	17.4 **[16.3-28.2]**	20.6 [19.7-22.7]	11.3 *[10.1-15.4]*	12.9 [12.0-14.4]	4.0 *[0.8-9.7]*
Submandibular gland L (Gy)	4.6 *[3.2-10.1]*	3.6 [3.3-3.6]	9.8 *[7.6-14.2]*	9.9 [8.1-11.1]	1.5 [0.2-4.6]
Submandibular gland R (Gy)	5.0 *[3.1-12.6]*	3.4 [3.4-3.5]	10.8 *[7.8-13.6]*	10.3 [8.4-11.2]	1.3 *[0.6-6.3]*
Thyroid (Gy)	28.5 [25.7-29.3]	17.0 *[13.6-19.4]*	13.0 **[5.6-24.6]**	15.3 **[7.0-19.7]**	0.8 *[0.3-10.1]*
Larynx + prox esophagus (Gy)	9.8 **[9.0-24.9]**	10.7 [9.7-11.6]	13.3 **[5.5-26.0]**	9.3 **[7.8-19.5]**	2.3 **[1.9-17.9]**
Heart (Gy)	13.4 [13.1-14.0]	8.1 [8.0-8.3]	6.9 *[5.7-10.9]*	9.4 [7.7-11.9]	0.01 [0.01-0.2]
Lung L (Gy)	4.1 [3.6-4.2]	7.0 [6.5-8.2]	7.9 [7.8-9.7]	6.9 [6.5-7.1]	2.0 [1.3-4.9]
Lung R (Gy)	8.6 [7.9-8.8]	8.6 [8.5-9.5]	10.2 [8.3-10.3]	9.4 [7.9-10.7]	2.3 [2.0-5.8]
Esophagus (Gy)	29.9 [29.7-31.3]	19.4 [18.8-20.5]	16.3 **[12.2-23.6]**	26.5 **[21.6-31.9]**	2.3 *[0.7-6.8]*
Intestines (Gy)	10.1 [9.9-10.2]	8.7 [8.3-8.7]	8.4 [6.6-12.0]	11.7 [7.7-12.0]	0.4 [0.1-0.5]
Pancreas (Gy)	17.1 [16.4-17.6]	12.1 [10.2-13.3]	8.7 *[8.5-15.4]*	13.7 [8.2-14.7]	0.0 [0.0-0.0]
Kidney L (Gy)	4.5 [4.2-4.8]	6.2 [5.2-9.8]	7.5 [5.8-9.0]	6.3 [5.7-6.8]	2.5 *[0.9-7.7]*
Kidney R (Gy)	3.3 [3.0-3.9]	5.3 [5.0-8.9]	5.6 [5.6-8.4]	6.1 [4.9-6.5]	2.3 [2.0-5.8]

* Differences per technique >10.0 Gy or between 5.0- 10.0 Gy are indicated in **bold** or *italic*, respectively.

Table 4. D_{1cc} (Gy) for organs at risk with individual techniques

D_{1cc} *OARs*	3D-CRT	IMRT	VMAT	Tomo	PBS
	Median [Range]	Median [Range]	Median [Range]	Median [Range]	Median [Range]
Scalp (Gy)	37.1 [36.2-38.0]	37.1 [36.8-37.8]	36.0 [35.3-37.5]	36.0 [35.3-36.3]	36.9 [35.8-37.7]
Lens L (Gy)	**9.4 [6.2-21.8]**	13.7 [13.0-13.8]	**10.8 [5.3-17.0]**	**11.7 [4.6-16.9]**	*3.7 [1.6-10.8]*
Lens R (Gy)	**13.7 [5.2-20.8]**	15.8 [15.2-16.0]	**10.3 [5.6-17.2]**	**12.9 [4.5-17.1]**	*3.6 [1.2-10.9]*
Parotid gland L (Gy)	36.5 [35.9-37.5]	36.5 [35.8-36.7]	*19.2 [18.9-23.6]*	23.6 [23.2-25.1]	**16.1 [14.4-31.1]**
Parotid gland R (Gy)	36.2 [36.0-37.4]	36.4 [36.0-37.7]	*20.8 [19.8-24.6]*	22.7 [22.0-24.9]	**13.3 [9.9-28.6]**
Submandibular gland L (Gy)	**9.1 [5.1-19.0]**	4.7 [3.6-8.4]	*17.0 [12.7-19.6]*	13.7 [10.9-15.0]	**10.9 [1.6-15.1]**
Submandibular gland R (Gy)	**17.6 [4.2-19.4]**	6.8 [6.4-10.5]	*14.9 [14.5-19.7]*	14.2 [12.1-15.6]	**9.5 [4.2-23.0]**
Thyroid (Gy)	30.7 [29.4-30.8]	*26.1 [20.7-27.7]*	**17.9 [14.5-30.1]**	**24.2 [13.6-28.6]**	**7.4 [5.6-25.8]**
Larynx + prox esophagus (Gy)	31.7 [30.2-31.8]	*30.1 [24.3-32.1]*	**20.2 [14.8-33.5]**	**24.7 [12.5-30.4]**	**17.5 [11.2-33.5]**
Heart (Gy)	29.1 [28.5-29.9]	15.1 [14.9-18.6]	11.7 [10.9-16.9]	**17.4 [14.0-24.4]**	0.3 [0.2-3.5]
Lung L (Gy)	33.0 [31.3-33.8]	*27.8 [25.8-30.4]*	27.2 [25.3-27.6]	*29.9 [25.1-31.1]*	*28.5 [26.4-33.7]*
Lung R (Gy)	33.1 [32.4-35.7]	28.3 [26.1-30.6]	28.4 [25.4-28.8]	*29.3 [27.6-33.0]*	*28.1 [27.8-33.6]*
Esophagus (Gy)	*32.4 [31.2-37.1]*	**32.1 [26.3-38.9]**	**22.6 [18.9-32.3]**	28.5 [26.5-31.1]	**13.6 [6.5-26.8]**
Intestines (Gy)	31.0 [28.8-32.3]	23.9 [23.1-24.7]	**17.7 [17.3-26.3]**	*27.4 [22.1-29.9]*	**11.4 [1.0-16.2]**
Pancreas (Gy)	**28.6 [27.5-39.4]**	*19.8 [15.5-23.9]*	**13.2 [11.0-21.9]**	**21.4 [10.3-24.7]**	0.1 [0.1-0.3]
Kidney L (Gy)	33.3 [32.7-33.3]	*24.2]19.2-28.8]*	**23.3 [14.9-25.9]**	*21.8 [21.0-26.6]*	**23.7 [20.3-34.3]**
Kidney R (Gy)	31.8 [29.4-32.3]	*21.7 [21.0-27.7]*	21.8 [19.7-23.0]	*22.5 [21.8-27.9]*	*23.2 [14.5-33.8]*

* Differences per technique >10.0 Gy or between 5.0- 10.0 Gy are indicated in **bold** or *italic*, respectively.

DISCUSSION

This multicenter dosimetric comparison of five different radiotherapy techniques (3D-CRT, IMRT, VMAT, Tomotherapyand PBS) currently applied for CSI demonstrates improved dose conformity and homogeneity of the target volume with all modern radiotherapy techniques compared with 3D-CRT, as well as a reduction in mean dose of >5.0 Gy to organs such as the thyroid, heart, esophagus, and pancreas. Compared to IMRT, VMAT, and Tomotherapy, an additional decrease in mean dose (>5.0 Gy) is found with PBS for lenses, parotid- and submandibular glands, larynx, thyroid, lungs, heart, intestines, stomach and pancreas. However, caution is needed in the interpretation of these results since ranges in mean dose for a number of OARs are wide per technique and also overlapping between different techniques. For example, the mean thyroid dose can range between 5.6 Gy and 24.6 Gy with VMAT and between 0.3 Gy and 10.1 Gy with PBS, depending on the treatment center.

In the literature several reports demonstrate improved CI and HI for the PTV and field-junctions by the use of modern radiotherapy techniques compared with 3D-CRT [11,13,17,35,36]. However, it should be mentioned that knowledge on the uncertainties related to possible motion of the target and correct target volume delineation are pre-requisites for highly-conformal techniques. The latter becomes relevant at the meningeal surfaces and cerebrospinal fluid in the dural reflections of the cranial nerves [37, 38].

In clinical practice, the reason for using more conformal techniques is better sparing of healthy tissue outside the planning target volume. However, nearly all published data on late toxicity after CSI concern neuro-cognitive decline, endocrinopathies, or growth retardation, in fact problems inherent to the treatment of the target volume [18-21]. In contrast, fewer results have been published on late toxicity outside the craniospinal target volume despite the use of the conventional 3D-CRT for decades [27-32]. As the introduction of modern radiotherapy techniques is of more recent date, it is still too early to be able to demonstrate a clinical benefit due to better sparing of the OARs surrounding the

craniospinal PTV. Nevertheless, for the thyroid, heart, lung, and pancreas, it may be relevant to improve organ sparing even at relatively low dose levels [21,29-32].

Techniques like IMRT, VMAT and Tomotherapy have the potential to decrease the dose to the thyroid, heart, esophagus and pancreas compared with 3D-CRT at the cost of a higher integral dose and therefore a higher potential risk of second malignancies induction. For this reason, an higher TNTV dose with modern photon techniques is often used as the argument for 3D-CRT continuation. Proton beam therapy is therefore very attractive, as it offers both high conformity and reduction of integral dose. In the literature several papers report on the estimated risk for secondary malignancies based on empirical models [e.g. 39]. However, the authors believe that this risk estimation should be based on clinical data. Unfortunately, very little clinical information on dose dependency for second malignancy induction is available. With a median follow-up of ten years, two reports on second malignancies after 3D-CRT have suggested tumor induction mainly within or adjacent to the PTV [27,28]. Therefore, it is uncertain whether a significant increase in second malignancies will be observed due to low dose irradiation to structures anterior to the vertebrae with modern photon techniques. However, although studies did not show that the unintended dose outside the target volume causes clinically significant side effects including secondary cancer, attempts should be made to keep dose to the OARs as low as possible. The same is true when administering protons by maximally limiting the scattered contribution from secondary neutrons, i.e. by preferably using PBS technology rather than passive scattered beams [40]. Additional reasons to refer patients for proton therapy are further dosimetric reductions in mean dose to the organs at risk compared to modern photon techniques. However, it might be questioned whether any clinical benefit will be observed if the doses received by the organs at risk remain far below the expected normal tissue tolerances [21,31, 41, 42]. Although the dosimetric outcome of this work is in favor of proton therapy and to a lesser extent of modern photon techniques, significant range in mean doses (up to

20 Gy) to the OARs are found between centers using a similar technique. This inter-center variation in mean doses to the OARs is larger than the differences in OARs doses reported by other published studies comparing irradiation techniques [12, 14, 35, 36]. On one hand, the large dose range points towards an effect of mastering a technique to a different extent, as already observed for VMAT dose distributions by Fogliata et al. [43]. On the other hand, these differences can be attributed to the choice of the optimization criteria made by the centers, prioritizing one objective over another (Table S1). For this planning study no fixed list of constraints for the OARs was provided to the participants in order to reflect daily practice in different centers using similar techniques. This means that in absence of an international guideline on dose-constraints for OARs related to CSI, a significant dose-range will persist between centers using similar techniques. However, this observation also impacts the potential benefit of one technique compared to another. Knowledge based planning systems could help reducing the differences in OAR sparing between institutions and techniques [44, 45].

As no consensus on dose constraints to vertebral bodies does exist at present time, an adolescent patient was chosen for this study to avoid discussions related to growth problems between centers. Including the vertebrae in the target volume will increase the dose to the structures antero-lateral of the vertebral bodies to some extent. However, it is not expected that the observations/conclusions from this study will alter by additional dose steering on the vertebrae. In addition, selecting an adolescent patient with a larger spinal target volume is technically more challenging.

Although we are aware of the fact that this work is based on the analysis of one patient only, we do not expect that expanding the number of patients will change our findings given the fact that the CSA target volume is quite consistent in between patients, and in relation to the surrounding structures [46]. The widest range of OARs mean doses for five different patients planned by VMAT at our department was 3 Gy. The latter value is smaller than the variation observed for some OARs in between centers using the same technique or in

between techniques. This observation supports the methodology of the study to focus on one patient for assessing inter-center variation as it reflects the daily reality for one patient. The variation in dosimetry could be reduced if the treatment planning exercise would have been repeated using the same constraints for all centers, as already demonstrated by Verbakel et al. [47], However, this re-optimization of the treatment planning technique does not reflect current situations across different centers and techniques.

For comparison purposes the same PTV margin was used for all techniques. We acknowledge that this uncertainty margin is inherent to a technique, equipment, and institutional protocols (e.g. patient immobilization methods, patient setup error correction protocols) [48]. Locally adopted PTV margins will have a potential impact on OARs dose in proximity of the target volume. However, it is expected that the found dosimetric range per institution and per technique will persist. Furthermore, the effect of patient (re)positioning uncertainties on the dose distribution has not been taken into account in this analysis. In fact, one technique might be more robust than another resulting in smaller detrimental effects on the ideal static dose distribution calculated by the treatment planning system [49-51]. Comparing the robustness of the different techniques is part of a future work. Finally, this is an in-silico treatment planning study and it has been demonstrated that a robust in-silico planning study may overestimate the potential dosimetric benefits of one technique over another [52,53].

CONCLUSION

Compared with 3D-CRT, modern radiotherapy techniques demonstrate a superior dose distribution often at the cost of a higher integral dose. With protons a further dosimetric reduction is observed for the OARs and integral body dose. Nevertheless, a wide range of doses to the OARs is found even between centers using similar techniques. In addition, an international guideline with dose constraints for CSI is essential to ensure comparable outcome between different centers.

REFERENCES

[1] Gajjar A, Chintagumpala M, Ashley D et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. Lancet Oncol 2006;7:813-20.

[2] Packer R, Gajjar A, Vezina G et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. J Clin Oncol 2006;24:4202-8.

[3] Lannering B, Rutkowski S, Doz F, et al. Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standard-risk medulloblastoma: results from the randomized multicenter HIT-SIOP PNET 4 trial. J Clin Oncol 2012;30:3187-93.

[4] Pizer BL, Weston CL, Robinson KJ et al. Analysis of patients with supratentorial primitive neuro-ectodermal tumours entered into the SIOP/UKCCSG PNET 3 study. Eur J Cancer 2006;42:1120-8.

[5] Calaminus G, Bamberg M, Jurgens H et al. Impact of surgery, chemotherapy and irradiation on long term outcome of intracranial malignant non-germinomatous germ cell tumors: results of the German Cooperative trial MAKEI 89. Klin Padiatr 2004;216:141-9.

[6] Chi SN, Zimmerman MA, Yao X at al. Intensive multimodality treatment for children with newly diagnosed CNS atypical teratoid rhabdoid tumor. J Clin Oncol 2009;27:385-9.

[7] Tekautz TM, Fuller CE, Blaney S et al. Atypical teratoid/rhabdoid tumors (ATRT): improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy. J Clin Oncol 2005;23:1491-9

[8] Merchant TE, Boop FA, Kun LE, Sanford RA. A retrospective study of surgery and reirradiation for recurrent ependymoma. Int J Radiat Oncol Biol Phys 2008;71:87-97.

[9] Parker WA, Freeman CR. A simple technique for craniospinal radiotherapy in the supine position. Radiother Oncol 2006;78:217-22.

[10] Tatcher M, Glicksman A. Field matching considerations in craniospinal irradiation. Int J Radiat Oncol Biol Phys 1989;17:865-9.

[11] Parker W, Filion E, Roberge D, Freeman CR. Intensity-modulated radiotherapy for craniospinal irradiation: target volume considerations, dose constraints, and competing risks. Int J Radiat Oncol Biol Phys 2007;69:251-7.

[12] Pai Panandiker A, Ning H, Likhacheva A, et al. Craniospinal irradiation with spinal IMRT to improve target homogeneity. Int J Radiat Oncol Biol Phys 2007;68:1402-9.

[13] Kusters JM, Louwe RJ, van Kollenburg PG, et al. Optimal normal tissue sparing in craniospinal axis irradiation using IMRT with daily intrafractionally modulated junction. Int J Radiat Oncol Biol Phys 2011;81:1405-14.

[14] Lee YK, Brooks CJ, Bedford JL, Warrington AP, Saran FH. Development and evaluation of multiple isocentric volumetric modulated arc therapy technique for craniospinal axis radiotherapy planning. Int J Radiat Oncol Biol Phys 2012;82:1006-12.

[15] Lopez Guerra JL, Marrone I, Jaen J, et al. Outcome and toxicity using helical tomotherapy for craniospinal irradiation in pediatric medulloblastoma. Clin Transl Oncol 2014;16:96-101.

[16] Chang EL, Allen P, Wu C, Ater J, Kuttesch J, Maor MH. Acute toxicity and treatment interruption related to electron and photon craniospinal irradiation in pediatric patients treated at the University of Texas M.D. Anderson Cancer Center. Int J Radiat Biol Phys 2002;52:1008-16.

[17] St Clair WH, Adams JA, Bues M, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. Int J Radiat Biol Phys 2004;58:727–34.

[18] Ris MD, Packer R, Goldwein J, Jones-Wallace D, Boyett. Intellectual outcome after reduced-dose radiation therapy plus adjuvant chemotherapy for medulloblastoma: a Children's Cancer Group Study. J Clin Oncol 2001;19:3470-6.

[19] Camara-Costa H, Resch A, Kieffer V, et al. Neuropsychological outcome of children treated for standard-risk medulloblastoma in the PNET-4 European randomized controlled trial of hyperfractionated versus standard radiation therapy and maintenance chemotherapy. Int J Radiat Oncol Biol Phys 2015;92:978-85.

[20] Yock TI, Yeap BY, Ebb DH, et al. Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study. Lancet Oncol 2016;17:287-98.

[21] Laughton SJ, Merchant TE, Sklar CA, et al. Endocrine outcomes for children with embryonal brain tumors after risk-adapted craniospinal and conformal primary-site irradiation and high-dose chemotherapy with stem-cell rescue on the SJMB-96 trial. J Clin Oncol 2008;25:1112-8.

[22] Thomas PR, Deutsch M, Kepner JL et al. Low-stage medulloblastoma: final analysis of trial comparing standard-dose with reduced-dose neuraxis irradiation. J Clin Oncol 2002;18:3004-11.

[23] Packer RJ, Goldwein J, Nicholson HS et al. Treatment of children with medulloblastoma with reduced-dose craniospinal radiation therapy and adjuvant chemotherapy: A Children's Cancer Group Study. J Clin Oncol 1999;17:2127-36.

[24] Carrie C, Muracciole X, Gomez F et al. Conformal radiotherapy, reduced boost volume, hyperfractionated radiotherapy, and online quality control in standard-risk medulloblastoma without chemotherapy: results of the French M-SFOP 98 protocol. Int J Radiat Oncol Biol Phys 2005;63:711-6.

[25] Vanuytsel L, Brada M. The role of prophylactic spinal irradiation in localized intracranial ependymoma. Int J Radiat Oncol Biol Phys 1991;21:825-30.

[26] Rogers SJ, Mosleh-Shirazi MA, Saran FH. Radiotherapy of localised intracranial germinoma: time to sever historical ties? Lancet Oncol 2005;6:509-19.

[27] Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. Neuro Oncol 2013;15:97-103.

[28] von Hoff K, Hinkes B, Gerber NU, et al. Long-term outcome and clinical prognostic factors in children with medulloblastoma treated in the prospective randomised multicentre trial HIT91. Eur J Cancer 2009;45:1209-17.

[29] Jakacki RI, Goldwein JW, Larsen RL, Barber G, Silber JH. Cardiac dysfunction following spinal irradiation during childhood. J Clin Oncol 1993;11:1033-8.

[30] Guldner L, Haddy N, Pien F et al. Radiation dose and long term risk of cardiac pathology following radiotherapy and anthracyclin for a childhood cancer. Radiother Oncol. 2006; 81:47-56.

[31] Jakacki RI, Schramm CM, Donahue BR, Haas F, Allen JC. Restrictive lung disease following treatment for malignant brain tumors: a potential late effect of craniospinal irradiation. J Clin Oncol 1995;13:1478-85.

[32] Nottage KA, Ness KK, Li C, Srivastava D, Robinson LL, Hudson MM. Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic leukaemia-from the St. Jude lifetime cohort. Br J Haematol 2014;165:364-74.

[33] van't Riet A, Mak AC, Moerland MA, Elders LH, van der Zee W, A conformation number to quantify the degree of conformality in brachytherapy and external beam irradiation: application to the prostate. Int J Radiat Oncol Biol Phys. 1997;37:731-6.

[34] Kataria T, Sharma K, Subramani V, Karrthick KP, and Bisht SS. Homogeneity Index: An objective tool for assessment of conformal radiation treatments. J Med Phys 2012;37: 207–213.

[35] Studenski MT, Shen X, Yu Y, et al. Intensity-modulated radiation therapy and volumetric-modulated arc therapy for adult craniospinal irradiation-a comparison with traditional techniques. Med Dosim 2013;38:48-54.

[36] Yoon M, Shin DH, Kim J, et al. Craniospinal irradiation techniques: a dosimetric comparison of proton beams with standard and advanced photon radiotherapy. Int J Radiat Oncol Biol Phys 2011;81:637-46.

524 [37] Noble DJ, Ajithkumar T, Lambert J, Gleeson I, Williams MV, Jefferies SJ, Highly
525 Conformal Craniospinal Radiotherapy Techniques Can Underdose the Cranial Clinical Target
526 Volume if Leptomeningeal Extension through Skull Base Exit Foramina is not Contoured. Clin
527 Oncol (R Coll Radiol) 2017 doi: 10.1016/j.clon.2017
528 [38] Carrie C, Hoffstetter S, Gomez F et al., Impact of targeting deviations on outcome in
529 medulloblastoma: study of the French Society of Pediatric Oncology (SFOP). Int J Radiat
530 Oncol Biol Phys. 1999; 45:435-9
531 [39] Ho ESQ, Barrett SA, Mullaney LM., A review of dosimetric and toxicity modeling of
532 proton versus photon craniospinal irradiation for pediatrics medulloblastoma. Acta Oncol.
533 2017; 56:1031-1042
534 [40] Taddei PJ, Mahajan A, Mirkovic D, et al. Predicted risks of second malignant neoplasm
535 incidence and mortality due to secondary neutrons in a girl and boy receiving proton
536 craniospinal irradiation. Phys Med Biol 2010;55:7067-80.
537 [41] Wolden SL. Protons for craniospinal radiation: Are clinical data important? Int J Radiat
538 Oncol Biol Phys 2013;78: 231–232.
539 [42] Brodin NP, Munck Af Rosenschold P, Aznar MC et al. Radiobiological risk estimates of
540 adverse events and secondary cancer for proton and photon radiation therapy of pediatric
541 medulloblastoma. Acta Oncol 2011; 50: 806-16
542 [43] A. Fogliata, S. Bergström, I. Cafaro, Cranio-spinal irradiation with volumetric
543 modulated arc therapy: A multi-institutional treatment experience. Radiother. Oncol., 99
544 (2011), pp. 79-85.
545 [44] Good D, Lo J, Lee WR, Wu QJ, Yin FF, Das SK. A knowledge-based approach to
546 improving and homogenizing intensity modulated radiation therapy planning quality among
547 treatment centers: an example application to prostate cancer planning, Int J Radiat Oncol
548 Biol Phys. 2013; 87(1):176-81;
549 [45] Tol JP, Delaney AR, Dahele M, Slotman BJ, Verbakel WFAR. Evaluation of a
550 388 knowledge-based planning solution for head and neck cancer. Int J Radiat Oncol Biol

389 Phys 2015;91:612–20

[46] Bandurska-Luque A, Piotrowski T, Skrobała A, Ryczkowski A, Adamska K[4], Kaźmierska J, Prospective study on dosimetric comparison of helical tomotherapy and 3DCRT for craniospinal irradiation - A single institution experience. Rep Pract Oncol Radiother. 2015 Jan 18;20(2):145-52.

[47] W.F.A.R. Verbakel,P.A. Doornaert,C.P. Raaijmakers,L. J. Bos, M. Essers, J.B.van de Kamer, C. H. Terhaard, J. H. Kaanders, National planning comparison results in improved plan quality for head and neck radiotherapy, Radiotherapy and Oncology, februari 2018, submitted.[48] ICRU report 83, Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy (IMRT). J ICRU 2010.

[49] Myers P, Stathakis S, Mavroidis P, Esquivel C, Papanikolaou N. Evaluation of localization errors for craniospinal axis irradiation delivery using volume modulated arc therapy and proposal of a technique to minimize such errors. Radiother Oncol 2013;108:107-13.

[50] Lin H, Ding X, Kirk M, et al. Supine craniospinal irradiation using a proton pencil beam scanning technique without match line changes for field junctions. Int J Radiat Oncol Biol Phys 2014; 90:71-8.

[51] Farace P, Bizzocchi N, Righetto R, et al. Supine craniospinal irradiation in pediatric patients by proton pencil beam scanning. Radiother Oncol 2017;123:112-8.

[52] Urie MM, Goitein M, Doppke K, et al. The role of uncertainty analysis in treatment planning. Int J Radiat Oncol Biol Phys 1991;21:91-107.

[53] Kraan AC, van de Water S, Teguh DN, et al. Dose uncertainties in IMPT for oropharyngeal cancer in the presence of anatomical, range, and setup errors. Int J Radiat Oncol Biol Phys 2013;87:888-96.

SUPPLEMENTARY MATERIAL

Table S1. Overview of the constraints used for the OARs per technique, and per center.

	Center	3D-CRT	IMRT	VMAT	Tomotherapy	PBS
Thyroid	1	No limit	Max EUD <12 Gy	D_{mean} <5-10 Gy	D_{max} < 15 Gy	No limit
	2	No limit	No limit	No limit	D_{mean} < 19.5 Gy	No limit
	3	No limit	No limit	No limit	D_{mean} ~6-20Gy	No limit
Larynx	1	No limit	Max EUD <10 Gy	D_{mean} <5-10 Gy	D_{max} < 15 Gy	No limit
	2	No limit	No limit	No limit	No limit	No limit
	3	No limit	No limit	No limit	No limit	No limit
Heart	1	No limit	Max dose <20 Gy	D_{mean} <5-8 Gy	D_{max} < 15 Gy	No limit
	2	No limit	No limit	No limit	D_{mean} < 14 Gy	No limit
	3	No limit	No limit	No limit	D_{mean} ~6-11Gy	No limit
Lungs	1	No limit	Max DVH 5% <20Gy	D_{mean} <5-10 Gy	D_{max} < 34 Gy	No limit
	2	No limit	No limit	No limit	D_{mean} < 12 Gy	No limit
	3	No limit	No limit	No limit	D_{mean} ~6-11Gy	No limit
Oesophagus	1	No limit	Max EUD <10 Gy	D_{mean} < 14 Gy	No limit	No limit
	2	No limit	No limit	No limit	D_{mean} < 33 Gy	No limit
	3	No limit	No limit	No limit	D_{mean} ~10-20Gy	No limit
Intestine+stomach	1	No limit	No limit	No limit	D_{max} < 30 Gy	No limit
	2	No limit	No limit	No limit	V40Gy < 100 %	No limit
	3	No limit	No limit	No limit	No limit	No limit
Pancreas	1	No limit	No limit	No limit	No limit	No limit
	2	No limit	No limit	No limit	No limit	No limit
	3	No limit	No limit	No limit	No limit	No limit
Kidneys	1	No limit	Max DVH 5% <20Gy V20 aim < 25%, accept < 35%	D_{mean} <5-8 Gy	D_{max} < 34 Gy	No limit No limit
	2	No limit	No limit	No limit	D_{mean} < 10 Gy	No limit
	3	No limit	No limit	No limit	D_{mean} ~4-7Gy	No limit
Sclap	1	No limit	Max EUD <12 Gy	No limit	No limit	No limit
	2	No limit	No limit	No limit	No limit	No limit
	3	No limit	No limit	No limit	No limit	No limit
Lens	1	No limit	Max EUD <10 Gy	D_{mean} < 12-14 Gy	D_{max} <4.5 Gy	D_{max}< 10Gy
	2	No limit	No limit	No limit	D_{mean} < 6 Gy	D_{mean} < 8Gy
	3	D_{mean}<10Gy	No limit	No limit	D_{mean} < 28 Gy	No limit
Parotid glands	1	No limit	Max dose <20 Gy	D_{mean} <5-10 Gy	D_{max} < 25 Gy	No limit
	2	No limit	No limit	No limit	D_{mean} < 12 Gy	No limit
	3	No limit	No limit	No limit	No limit	No limit
Submandibularis glands	1	No limit	Max DVH 5% <20Gy	D_{mean} <5-10 Gy	No limit	No limit
	2	No limit	No limit	No limit	D_{mean} < 12 Gy	No limit
	3	No limit	No limit	No limit	No limit	No limit

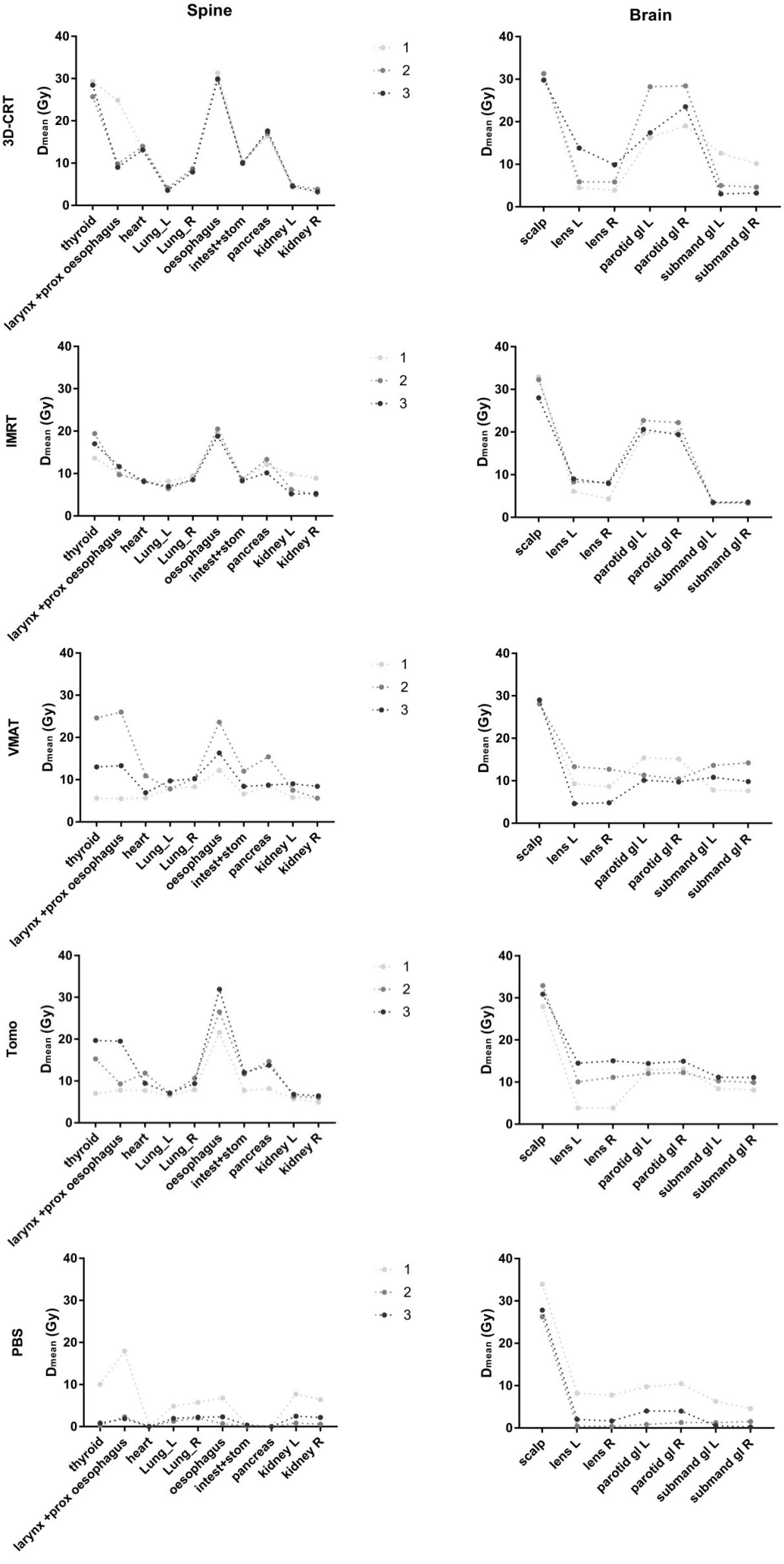
Spine
Brain
3D-CRT
IMRT
VMAT
Tomo
PBS
Dmean (Gy)
1
2
3
thyroid
larynx +prox oesophagus
heart
Lung_L
Lung_R
oesophagus
intest+stom
pancreas
kidney L
kidney R
scalp
lens L
lens R
parotid gl L
parotid gl R
submand gl L
submand gl R

Figure S1. D_{mean} (Gy) for the organs at risk surrounding the brain and the spine per technique and per center.

[Tomo: Tomotherapy; PBS: proton pencil beam scanning].

LEGEND OF THE FIGURES

Figure 1

Craniospinal axis dose distribution with photons (3D-CRT, IMRT, VMAT, Tomotherapy) and protons. Only one out of three generated plans per technique is depicted.

Figure 2:

CI, HI, D2% and D98% of the PTV_{brain} and PTV_{spine} per center and per technique [Tomo: Tomotherapy; PBS: proton pencil beam scanning].

Figure 3:

Median D_{mean} (Gy) for the organs at risk surrounding the brain (A) and the spine (B). Error bars show the range (min, max) per technique [Tomo: Tomotherapy; PBS: proton pencil beam scanning].

Figure S1:

D_{mean} (Gy) for the organs at risk surrounding the brain and the spine per technique and per center. [Tomo: Tomotherapy; PBS: proton pencil beam scanning].