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## 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<sup>a</sup>, Mirjam Bosman<sup>a</sup>, Yasmin Lassen-Ramshad<sup>b</sup>, Anne Vestergaard<sup>b</sup>, Foppe Oldenburger<sup>c</sup>, Jorrit Visser<sup>c</sup>, Efi Koutsouveli<sup>d</sup>, Chryssa Paraskevopoulou<sup>d</sup>, Gail Horan<sup>e</sup>, Thankamma Ajithkumar<sup>e</sup>, Beate Timmermann<sup>f</sup>, Carolina-Sofia Fuentes<sup>f</sup>, Gillian Whitfield<sup>g</sup>, Thomas Marchant<sup>h</sup>, Laetitia Padovani<sup>i</sup>, Eloise Garnier<sup>i</sup>, Lorenza Gandola<sup>j</sup>, Silvia Meroni<sup>j</sup>, Bianca A. W. Hoeben<sup>k</sup>, Martijn Kusters<sup>k</sup>, Claire Alapetite<sup>l</sup>, Sandra Losa<sup>l</sup>, Farid Goudjil<sup>l</sup>, Henriette Magelssen<sup>m</sup>, Morten Egeberg Evensen<sup>m</sup>, Frank Saran<sup>n</sup>, Gregory Smyth<sup>o</sup> , Barbara Rombi<sup>p</sup>, Roberto Righetto<sup>p</sup>, Rolf-Dieter Kortmann<sup>q</sup> and Geert O. Janssens<sup>a</sup>

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### ABSTRACT

**Purpose:** Conventional techniques (3D-CRT) for craniospinal irradiation (CSI) are still widely used. Modern techniques (IMRT, VMAT, TomoTherapy<sup>®</sup>, 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 and methods:** A multicenter ( $n = 15$ ) dosimetric analysis of five different techniques for CSI (3D-CRT, IMRT, VMAT, TomoTherapy<sup>®</sup>, PBS; 3 centers per technique) was performed using the same patient data, set of delineations and dose prescription (36.0/1.8 Gy). 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  $>10.0$  Gy were observed with PBS compared to modern photon techniques for parotid glands, thyroid and pancreas. Following this technique, a wide range in dosimetry among centers using the same technique was observed (e.g., thyroid mean dose: VMAT: 5.6–24.6 Gy; PBS: 0.3–10.1 Gy).


**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.

### ARTICLE HISTORY

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 Supplemental data for this article can be accessed [here](#).

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## 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 photon 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<sup>®</sup> 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.

## Material and methods

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, IA, USA), vacuum mattress (BlueBag<sup>TM</sup> 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<sub>brain</sub>) and the spinal levels C1-L2 (PTV<sub>spine</sub>), and of 8 mm for the levels L3-S3 (PTV<sub>spine</sub>). PTV<sub>total</sub> is defined as the combination of PTV<sub>brain</sub> and PTV<sub>spine</sub>. 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<sub>total</sub>.

## Treatment planning

The radiotherapy department of the University Medical Center Utrecht, The Netherlands, sent the CT-scan with contours to 14 additional SIOP-E-linked institutes participating in this study. Each center used either 3D-CRT, IMRT, VMAT, TomoTherapy<sup>®</sup> (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<sub>total</sub> coverage (at least 95% of PTV<sub>total</sub> 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.

### 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<sub>total</sub>, PTV<sub>brain</sub> and PTV<sub>spine</sub>) 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):

$$CI = \frac{(V_{95\%}^{PTV})^2}{V^{PTV} \times V_{95\%}}$$

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

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  $\geq 5.0$  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.

#### Conformity and homogeneity

The median CI for the PTV<sub>total</sub> 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<sub>total</sub> was similar for all techniques when considering the range of data per technique; however, better median HI values for PTV<sub>spine</sub> were observed with modern radiotherapy techniques (Table 2).

In particular, for the 3D-CRT technique, hot spots within the PTV<sub>spine</sub> ( $V_{107\%}$ : 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<sub>brain</sub> was found for IMRT (0.8–1.0) and PBS (0.7–0.9). For the CI of the PTV<sub>spine</sub>, 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  $D_{2\%}$  (PTV<sub>brain</sub>: 36.4–40.0 Gy; PTV<sub>spine</sub>: 36.4–39.6) while VMAT dose distributions in  $D_{98\%}$  (PTV<sub>brain</sub>: 33.7–35.5 Gy; PTV<sub>spine</sub>: 33.7–35.2 Gy) (Figure 2 and Table 2).

#### Normal tissue sparing

Compared with 3D-CRT, a decrease in the mean dose to the thyroid by more than 10.0 Gy (28.5 Gy vs. 15.1\* Gy)

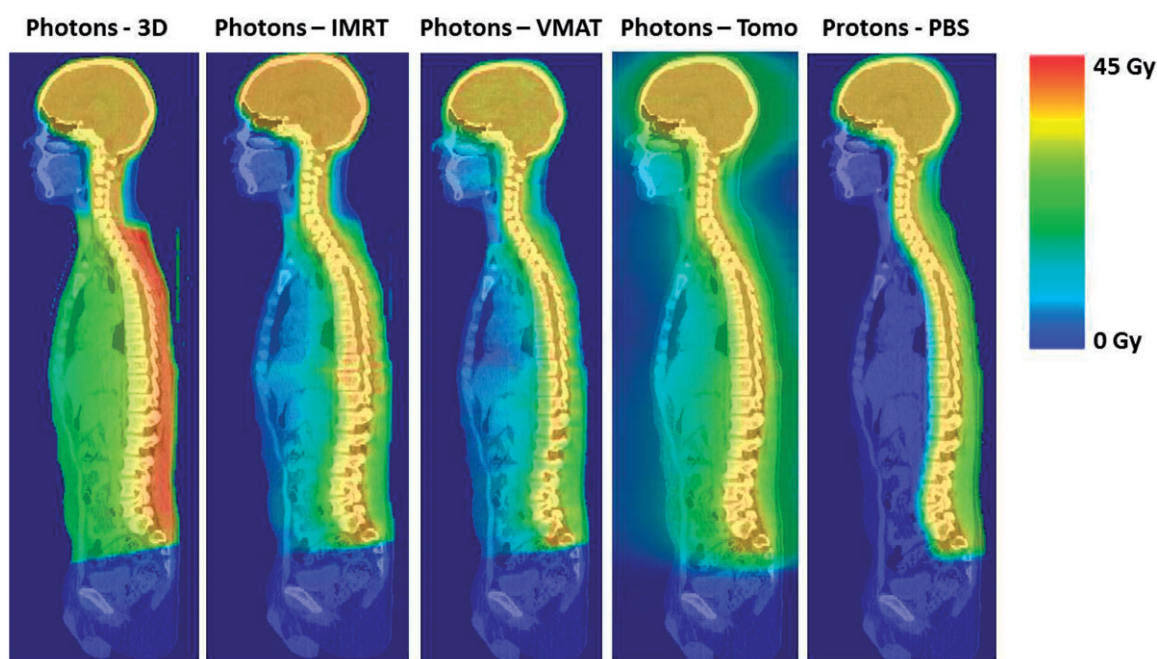


Figure 1. Craniospinal axis dose distribution with photons (3D-CRT, IMRT, VMAT, Tomotherapy) and protons. Only one out of three generated plans per technique is depicted.

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

	3D-CRT Median [Range]	IMRT Median [Range]	VMAT Median [Range]	Tomo Median [Range]	PBS Median [Range]
<b>PTV total dosimetry</b>					
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]
D <sub>mean</sub> (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]
<b>PTV brain dosimetry</b>					
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]
D <sub>mean</sub> (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]
<b>PTV spine dosimetry</b>					
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]
D <sub>mean</sub> (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]
<b>TNTV</b>					
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.

(\* represents average of the D<sub>mean</sub> median value of the three modern photon techniques). was observed for all modern photon radiotherapy techniques, while a decrease between 5.0 and 10.0Gy for the mean dose of both parotid glands (20.5Gy vs. 14.9\* Gy), heart (13.4Gy vs. 8.1\* Gy), esophagus (29.9Gy vs. 20.7\* Gy) and pancreas (17.1Gy vs. 11.5\* Gy) was seen (Figure 3, Table 3).

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

When comparing one specific radiotherapy technique among the three participating centers, a wide range in mean doses delivered to the OARs was found (Table 3). Ranges of >10.0Gy were observed for the lenses (Tomotherapy), thyroid (VMAT, Tomotherapy), larynx + proximal esophagus (3D-CRT, VMAT, Tomotherapy, PBS) and esophagus (VMAT, Tomotherapy). Differences larger than 10Gy for D1cc between centers applying the same technique were even more frequent (Table 4). D<sub>mean</sub> ranges between 5.0 and 10.0Gy were seen for the lenses (3D-CRT, VMAT, PBS), parotid and submandibular glands (3D-CRT, VMAT, PBS), thyroid

(IMRT, PBS), heart (VMAT), intestines-stomach, pancreas and esophagus (VMAT, Tomotherapy), and kidneys (PBS). The range in mean doses for OARs of the spine was the narrowest for 3D-CRT.

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<sub>mean</sub> for all OARs, considered in the manuscript, is 3Gy (data not shown).

## Discussion

This multicenter dosimetric comparison of five different radiotherapy techniques (3D-CRT, IMRT, VMAT, Tomotherapy and 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 >5.0Gy to organs such as the thyroid, heart, esophagus and pancreas. Compared to IMRT, VMAT and Tomotherapy, an additional decrease in mean dose (>5.0Gy) 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



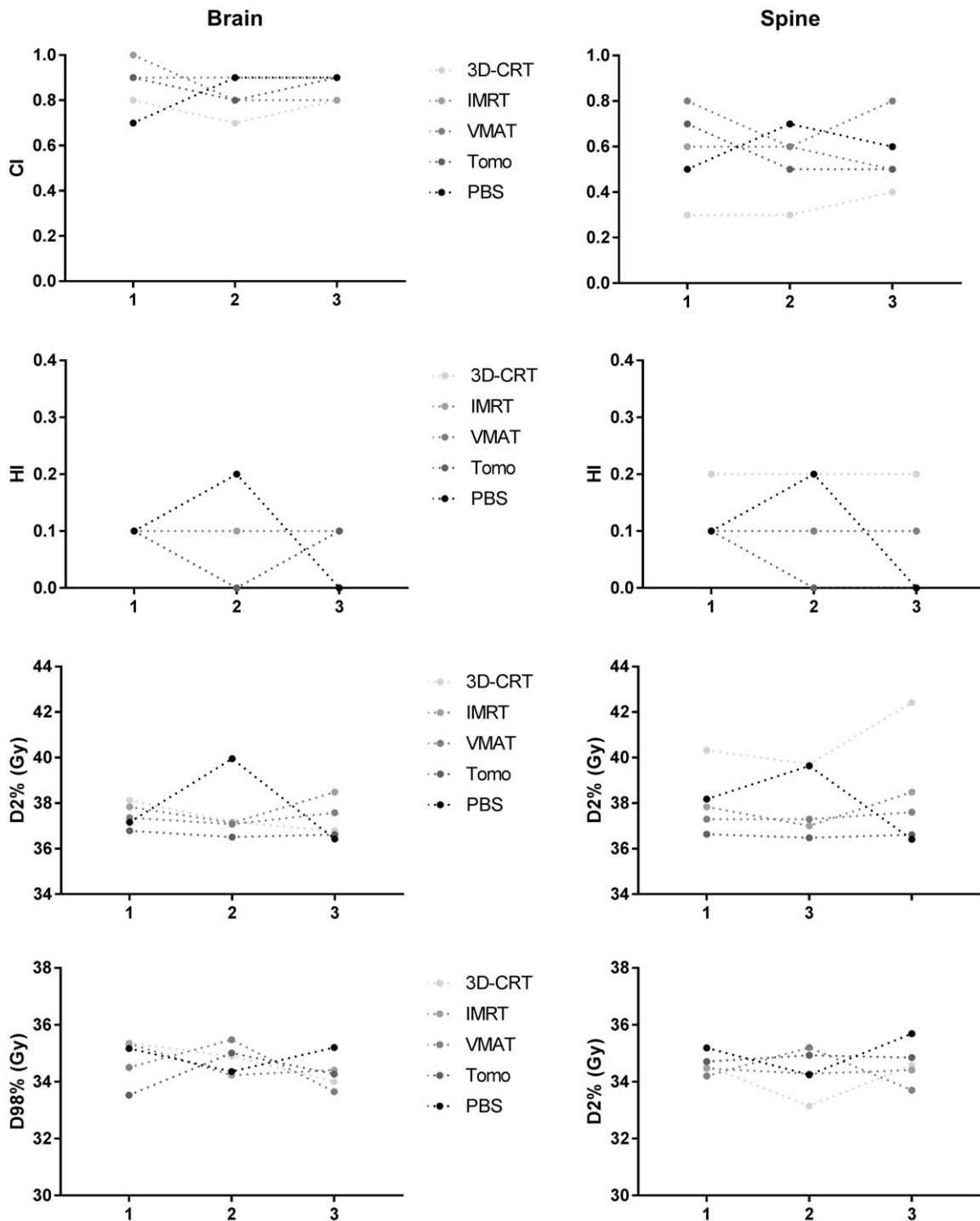


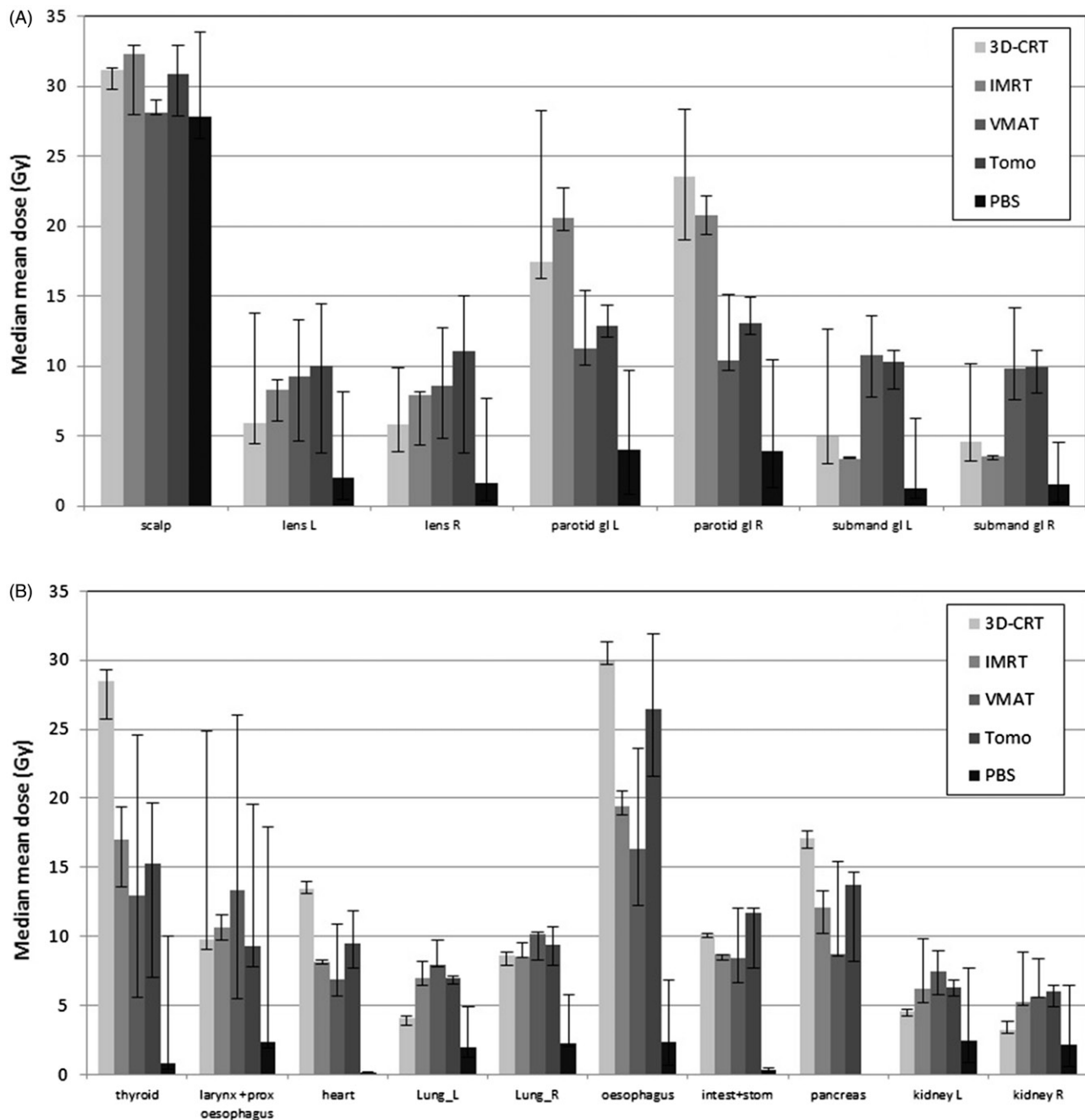
Figure 2. CI, HI, D2% and D98% of the PTV<sub>brain</sub> and PTV<sub>spine</sub> per center and per technique. [Tomo: Tomotherapy; PBS: proton pencil beam scanning].

and also overlapping between different techniques. For example, the mean thyroid dose can range between 5.6 and 24.6 Gy with VMAT and between 0.3 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



**Figure 3.** Median  $D_{\text{mean}}$  (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].

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, a 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 10 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

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

$D_{\text{mean}}$ 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 >10.0Gy or between 5.0 and 10.0Gy are indicated in **bold** or *italic*, respectively.

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

$D_{1\text{cc}}$ 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)	<b>9.4 [6.2–21.8]</b>	13.7 [13.0–13.8]	<b>10.8 [5.3–17.0]</b>	<b>11.7 [4.6–16.9]</b>	3.7 [1.6–10.8]
Lens R (Gy)	<b>13.7 [5.2–20.8]</b>	15.8 [15.2–16.0]	<b>10.3 [5.6–17.2]</b>	<b>12.9 [4.5–17.1]</b>	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]	<b>16.1 [14.4–31.1]</b>
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]	<b>13.3 [9.9–28.6]</b>
Submandibular gland L (Gy)	<b>9.1 [5.1–19.0]</b>	4.7 [3.6–8.4]	17.0 [12.7–19.6]	13.7 [10.9–15.0]	<b>10.9 [1.6–15.1]</b>
Submandibular gland R (Gy)	<b>17.6 [4.2–19.4]</b>	6.8 [6.4–10.5]	14.9 [14.5–19.7]	14.2 [12.1–15.6]	<b>9.5 [4.2–23.0]</b>
Thyroid (Gy)	30.7 [29.4–30.8]	26.1 [20.7–27.7]	<b>17.9 [14.5–30.1]</b>	<b>24.2 [13.6–28.6]</b>	7.4 [5.6–25.8]
Larynx + prox esophagus (Gy)	31.7 [30.2–31.8]	30.1 [24.3–32.1]	<b>20.2 [14.8–33.5]</b>	<b>24.7 [12.5–30.4]</b>	<b>17.5 [11.2–33.5]</b>
Heart (Gy)	29.1 [28.5–29.9]	15.1 [14.9–18.6]	11.7 [10.9–16.9]	<b>17.4 [14.0–24.4]</b>	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]	<b>32.1 [26.3–38.9]</b>	<b>22.6 [18.9–32.3]</b>	28.5 [26.5–31.1]	<b>13.6 [6.5–26.8]</b>
Intestines (Gy)	31.0 [28.8–32.3]	23.9 [23.1–24.7]	<b>17.7 [17.3–26.3]</b>	27.4 [22.1–29.9]	11.4 [1.0–16.2]
Pancreas (Gy)	<b>28.6 [27.5–39.4]</b>	19.8 [15.5–23.9]	<b>13.2 [11.0–21.9]</b>	<b>21.4 [10.3–24.7]</b>	0.1 [0.1–0.3]
Kidney L (Gy)	33.3 [32.7–33.3]	24.2 [19.2–28.8]	<b>23.3 [14.9–25.9]</b>	21.8 [21.0–26.6]	<b>23.7 [20.3–34.3]</b>
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 >10.0Gy or between 5.0 and 10.0Gy are indicated in **bold** or *italic*, respectively.

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 the 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.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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