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Cochlear-optimized treatment planning in photon and proton radiosurgery for vestibular schwannoma patients

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ABSTRACT

Objective: To investigate the potential to reduce the cochlear dose with robotic photon radiosurgery or intensity-modulated proton therapy planning for vestibular schwannomas.
Materials and Methods: Clinically delivered photon radiosurgery treatment plans were compared to five cochlear-optimized plans: one photon and four proton plans (total of 120). A 1x12 Gy dose was prescribed. Photon plans were generated with Precision (Cyberknife, Accuray) with no PTV margin for set-up errors. Proton plans were generated using an in-house automated multi-criterial planning system with three or nine-beam arrangements, and applying 0 or 3 mm robustness for set-up errors during plan optimization and evaluation (and 3 % range robustness). The sample size was calculated based on a reduction of cochlear Dmean > 1.5 Gy(RBE) from the clinical plans, and resulted in 24 patients.
Results: Compared to the clinical photon plans, a reduction of cochlear Dmean > 1.5 Gy(RBE) could be achieved in 11/24 cochlear-optimized photon plans, 4/24 and 6/24 cochlear-optimized proton plans without set-up robustness for three and nine-beam arrangement, respectively, and in 0/24 proton plans with set-up robustness. The cochlea could best be spared in cases with a distance between tumor and cochlea. Using nine proton beams resulted in a reduced dose to most organs at risk.
Conclusion: Cochlear dose reduction is possible in vestibular schwannoma radiosurgery while maintaining tumor coverage, especially when the tumor is not adjacent to the cochlea. With current set-up robustness, proton therapy is capable of providing lower dose to organs at risk located distant to the tumor, but not for organs adjacent to it. Consequently, photon plans provided better cochlear sparing than proton plans.

1. Introduction

Vestibular schwannomas are benign nerve sheath tumors arising from the vestibular nerve in the internal acoustic canal and/or cerebellopontine angle. Early symptoms comprise hearing loss, tinnitus, dizziness and/or unsteadiness [1]. When a vestibular schwannoma is large or demonstrates tumor progression, treatment is required to prevent further loss of function and even mortality due to the mass effect of the tumor. For patients with a small to medium-sized tumor (extracanalicular diameter less than 3 cm) both surgery and fractionated stereotactic radiotherapy or radiosurgery are viable options, with tumor control rates ranging between 90 and 100 %, depending on the size of the tumor [2–4]. In this patient group, the choice of treatment is partly based on the potential side-effects, such as hearing loss. Radiotherapy is increasingly used as a management option for small to medium-sized tumors with the goal of halting tumor progression and preventing

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Table 1
Dose specifications for photon and proton plans.

Structure	Constraint	Objective	Specifics in photon planning	Specifics in proton planning
Tumor (GTV = PTV)	≥ 98 % coverage at 12 Gy Prescription isodose 80 %	–	GTV Dmin ≥ 11 Gy	GTV Dmin ≥ 12 Gy(RBE) *(constraint)* GTV Dmax ≤ 15 Gy(RBE)
Optimization structures around or within the GTV	–	–	3 cm ring around GTV Dmax < 2 Gy	Optimization volumes: 0–5 mm ≤ 1 Gy(RBE); 5–10 mm ≤ 7 Gy(RBE); 29–31 mm ≤ 0.5 Gy(RBE); 'GTV-X' (see suppl.)
Paddick's Conformity Index	–	>0.77	–	–
Brainstem	≤12.5 Gy	–	Dmax in photon planning*	Optimization volume 10 mm expansion of GTV within the brainstem ≤ 12.5 Gy(RBE)
Cochlea	–	Dmean ALARA	–	Dmean ≤ 1 Gy(RBE)
Internal acoustic canal	–	Optimization of dose gradient	–	–
Trigeminal nerve	Dmax < 15 Gy	–	Dmax < 15 Gy	Dmax ≤ 5 Gy(RBE)
Eyes, optic nerves/chiasm, pituitary gland	–	Dmax < 2 Gy	No bundles through these structures in photons	Dmax ≤ 0.5 Gy(RBE) *(constraint)*
Other				- Avoid air filled mastoid spaces - Dmean whole brain ≤ 0.1 Gy(RBE)

Abbreviations: ALARA = as low as reasonably possible, Dmean = mean dose, Dmax = point maximum dose, Dmin = point minimum dose, Dnear-max = D_{35mm3}, GTV = gross tumor volume.
*Point Dmax was used in the photon planning software, while the Dnear-max (D_{35mm3}) was used in proton therapy; a deviation of 0.2 Gy(RBE) in the proton voxel-wise maximum (VWmax) scenario was deemed acceptable.

further loss of function [5].

Unilateral hearing loss and tinnitus have a substantial impact on patients' social lives and overall well-being and are therefore an important aspect in vestibular schwannoma management [6,7]. Studies have repeatedly demonstrated that hearing loss is correlated with higher doses of radiation to the cochlea, although there is currently no established threshold for mean cochlear dose in radiosurgery [8–12].

Previous research on the use of photon or proton therapy for treating vestibular schwannomas has not fully explored the potential of cochlear sparing strategies, for example by not specifically focusing on cochlea optimization during treatment planning or by utilizing passive scattering techniques (in proton therapy) [13–15]. Thus, there could be a potential to reduce the dose to the cochlea and surrounding tissues with current advanced radiation therapy technologies such as robotic radiosurgery with CyberKnife and intensity-modulated proton therapy (IMPT). Robotic photon radiosurgery with CyberKnife (Accuray Incorporated, Sunnyvale, California) consists of a maneuverable robotic radiotherapy unit, which offers a large number of beams and real-time image (X-ray) verification during treatment [16]. IMPT, on the other hand, utilizes the physical property of proton therapy to deliver a sharp dose fall-off at the end of the proton range, which is known as the Bragg peak [17].

A previous study comparing Linac-based (BrainLAB) to robotic radiosurgery (CyberKnife) found better cochlea-sparing for robotic radiosurgery [18]. Another study comparing different photon modalities to proton radiotherapy in large vestibular schwannomas and other benign tumors found superiority for fractionated proton therapy in terms of conformity and dosages to organs at risk, although they did not specifically assess the dose to the cochlea [19]. Previous treatment planning studies have not specifically focused on reducing the cochlear dose. Additionally, CykberKnife and IMPT treatment planning have not yet been compared. The objective of this study was to investigate the potential to reduce the cochlear dose with state-of-the-art robotic photon radiosurgery or with modern proton radiotherapy technology.

2. Materials and methods

In this study, we selected 24 consecutive patients who underwent robotic photon radiosurgery for vestibular schwannomas after September 2019. At our center, patients with progressive tumors or large tumors are offered active therapy. All patients provided informed consent. The study protocol was deemed exempt from the rules laid down in the Medical Research Involving Human Subjects Act (non-WMO) by the Erasmus MC's ethical committee (MEC-2021-0102). All included participants were treated at one center. The authors collaborated across different centers.

Clinical treatment plans, which were not optimized for cochlear dose, were compared to five cochlear-optimized treatment plans, consisting of one photon and four proton treatment plans. The proton treatment plans were generated using three or nine-beam arrangements (hereafter called three-beam and nine-beam proton therapy plans).

The photon radiosurgery treatment plans were manually generated using Precision (Accuray Inc., Sunnyvale, USA) and followed local protocols (Table 1) (8, 20). As in clinical practice, photon treatment plans were generated without adding a PTV margin to account for set-up or other geometrical errors [20]. A dose of 12 Gy was prescribed to the 80 % isodose line with a maximum dose of 15 Gy (100 % isodose line).

Proton treatment plans were generated using an in-house system for automated multi-criterial treatment planning called Erasmus-iCycle (see supplemental material A) [21]. Pareto-optimal plans with clinically favourable trade-offs between all treatment objectives were realized using an optimization protocol guided by a "wish-list" containing hard constraints and prioritized objectives (supplementary Table A.1). Robustness was achieved by minimax robust optimization with 29 scenarios [22–24]. Set-up errors were modelled by laterally shifting the proton pencil beams, while range errors were modelled by adjusting the CT Hounsfield units. All proton plans included 3 % range robustness. The range robustness setting (3 %) and set-up robustness setting (3 mm) were based on the accuracy of the treatment as measured at HollandPTC, which are also used clinically for intracranial treatments [25]. Following the DUPROTON protocol, robust optimized dose distributions resulted in three evaluation scenarios: nominal, voxel-wise minimum (VWmin), and voxel-wise maximum (VWmax) [26]. To investigate the potential of proton therapy to achieve the same level of geometrical accuracy as with robotic photon radiosurgery, we also made plans with a robustness setting of 0 mm. A relative biological effectiveness (RBE) of protons to photons of 1.1 was assumed to enable a better comparison of biological effect between the two treatment modalities [27].

Consequently, the unit Gy(RBE) was used for the proton plans.

Further details of the constraints, objectives, and optimization structures for treatment planning, including proton beam angle selection, are summarized in Table 1, and described in supplemental material A [20,28,29]. For the tumor and OAR, original (clinical) delineations were used [30].

To assess the acceptability of the proton treatment plans, we verified that clinical targets were met in VWmin, and OAR constraints were met in VWmax. The hard constraints were verified using the modality-specific planning system: Precision for the photon treatment plans and ErasmusMC RTStudio for proton treatment plans.

The primary endpoint was the cochlear Dmean. Secondary endpoints included Dmean, Dmedian, Dnear-max, and Dmin of the GTV and all OARs. Following ICRU-91 guidelines, Dnear-max = D_{35mm3} [28]. Additionally, the Paddick's conformity index (PCI), heterogeneity index (HI), and Gradient Index (GI) were evaluated for the GTV and the volumes receiving 1, 2, 3, 4, 6, 8, 10 Gy(RBE) were also evaluated [28,31,32]. Paddick's conformity index is an adjustment of the conformity index that takes into account whether the volume receiving 12 Gy (RBE) actually is located within the GTV. It is calculated by multiplying the volume receiving 12 Gy(RBE) with the GTV and consequently dividing this result by the squared multiplication of the volume receiving 12 Gy(RBE) within the tumor and the GTV. The heterogeneity index (Gy[RBE]) assesses dose heterogeneity within the tumor by subtracting the $D_{98\%}$ from $D_{2\%}$ and dividing this by $D_{50\%}$[32]. The gradient index is the ratio between the volume of dose receiving 6 Gy(RBE) to the volume receiving 12 Gy(RBE).

A sample size calculation was conducted with the aim of achieving a mean cochlear dose improvement > 1.5 Gy, resulting in the inclusion of 24 patients in this study. This was based on a previous publication that found this cut-off value predictive of better hearing outcomes [10]. This study used the dose to the modiolus, which shows a high inherent functional relationship to the mean cochlear dose [33]. The cochlear Dmean, brainstem Dnear-max/Dmedian, trigeminal nerve Dnear-max/Dmean of the different treatment plans were compared to the clinical photon plan by a paired *t*-test or the Wilcoxon's signed rank test (depending on the normality of the data), using p-value < 0.05 for statistical significance. The nominal, VWmin, and VWmax doses of the proton therapy treatment plans were recorded. The nominal dose parameters were used for the OAR comparisons. The number of statistical tests was limited to prevent problems with multiple testing, such as type I errors. Therefore, next to the cochlear Dmean, only certain parameters that were considered likely to show differences between the plans were included for statistical testing (brainstem Dnear-max/Dmedian and the trigeminal nerve Dnear-max/Dmean). A linear regression model was calculated for cochlear the Dmean and the tumor to cochlear distance.

Table 2
Patient and tumor characteristics.

Patients	N=24
Age, mean (range)	65 years (43 – 80)
N, male (%)	10 (42 %)
Koos grade, N (%)	0 (0 %)
I: intracanalicular tumor	3 (12 %)
II: extracanalicular; not abutting the brainstem	21 (88 %)
III: extracanalicular; abutting the brainstem	0 (0 %)
IV: extracanalicular; displacing the brainstem	
Extracanalicular tumor diameter, median (range)	17 mm (range 9 – 26 mm)
Tumor volume, median (range)	2.8 cc (1.2 – 7.9 cc)
Cochlea-tumor distance, median (range)	0 mm (range 0 – 7 mm)
Intracochlear tumor, N (%)	2 (8 %)
Volume of cochlea, mean (SD)	0.13 cc (0.03 cc)
Estimated extension in IAC, median (range)	100 % (15 % - 100 %)
Laterality, % left	42 %
Previous tumor resection*, N (%)	2 (8 %)

3. Results

Patient characteristics are shown in Table 2. All treatment plans met the hard constraints, except for one proton plan in which the brainstem Dnear-max was 13.0 Gy(RBE) (nominal scenario). The mean PCIs were relatively similar between the clinical and cochlear-optimized photon radiosurgery plans and the three or nine-beam proton plans without set-up robustness (0.85, 0.83, 0.78, and 0.82 respectively) (Table 3). The addition of set-up robustness to the proton plans resulted in a deterioration of the PCIs to 0.40 and 0.44 (for three and nine-beam plans, respectively).

For the photon plans, the cochlea optimization did not alter the GTV dose distributions, with the exception of the GTV Dmin (11.0 vs. 10.9 Gy in the cochlear-optimized plan [paired *t*-test, p = 0.06]) and the gradient index (4.5 vs. 4.6 Gy; p = 0.2) (Table 3).

The intended target dose inhomogeneity of the photon treatment plans could not fully be achieved in the proton therapy treatment plans due to an associated increase in the maximum dose to the brainstem, which is a hard constraint. As a result, compared to the photon plans, the proton plans showed lower GTV Dmean, Dnear-max, and heterogeneity index (ranges: 12.6 – 12.9 Gy(RBE); 13.2–14.4 Gy(RBE); 0.06–0.15, respectively - all nominal plans) (Table 3). The proton therapy treatment plans that included set-up robustness exhibited a lower heterogeneity index than the treatment plans without set-up robustness, as otherwise the brainstem Dnear-max constraint would have been violated.

Cochlear dose volume histograms are depicted in Fig. 1. The cochlear-optimized photon plans were found to be the most effective in reducing the median cochlear Dmean compared to the clinical plans (9.8 vs. 8.7 Gy; Wilcoxon signed rank test p < 0.01) (Table 3). In particular, eleven cochlear-optimized photon plans improved the cochlear Dmean by at least 1.5 Gy; the mean improvement in this group was 2.5 Gy and the average Dmean was 5.7 Gy (standard deviation: 2.4) (Fig. 2). A greater distance between the tumor and the cochlea resulted in a lower cochlear dose (Fig. 3). The cochlear Dmean was significantly correlated to the distance between the tumor and the cochlea in linear regression mode (R^2 = 62 %): $CochlearDmean = 10.5 - 1*mm\ distance$. This relation is also apparent in Supplementary Figure B.1.

The nine-beam proton plans (without set-up robustness) also improved the clinical cochlear Dmean, though this difference was not statistically significant (9.8 vs. 9.5 Gy(RBE), p = 0.41) (Table 3). In terms of cochlear Dmean, the nine-beam proton plans provided lower doses compared to the three-beam plans (9.5 vs. 9.9 Gy(RBE); Wilcoxon signed ranks test p = 0.41). Four of the three-beam proton plans showed an improvement of the cochlear Dmean greater than 1.5 Gy(RBE): The mean improvement in nominal scenario was 2.1 Gy(RBE) and the average Dmean was 5.1 Gy(RBE) (standard deviation: 2.0 Gy[RBE]). The nine-beam proton plans without set-up robustness performed better, as six plans showed an improvement of the cochlear Dmean greater than 1.5 Gy(RBE): the mean improvement in this group was 2.1 Gy(RBE) and the average Dmean was 5.5 Gy(RBE) (standard deviation: 2.1). However, when the 3 mm set-up robustness was used for the proton plans, no plan showed an improvement greater than 1.5 Gy(RBE) compared to the clinical treatment plan. The differences in cochlear Dmean across the error scenarios were small (0.2/0.3 Gy[RBE]), which indicates a relatively small impact of treatment uncertainties on the expected cochlear dose. The brainstem Dnear-max of the photon plans had a statistically significant lower dose compared to the proton plans (paired *t*-test p < 0.001). On the other hand, proton plans exhibited better brainstem Dmedian values with a mean of 0.2 Gy(RBE) without set-up robustness and 0.7 Gy(RBE) with set-up robustness, compared to 1.9 Gy in both photon plans (paired *t*-test p < 0.001) (Table 3).

Isodose values, which represent the volume of the brain receiving a specific dose (e.g., 1, 2, 3, 4, 6, 8, or 10 Gy[RBE]), were utilized to evaluate the dose distribution to the surrounding tissue (Table 3). The nine-beam proton plans without set-up uncertainty exhibited better (smaller) isodose volumes ≤ 4 Gy(RBE) compared to the photon plans,

Table 3
Dosimetric data.

		Photon radiosurgery 0 mm PTV margin		Three beam proton radiosurgery 0 mm set-up robustness			Three beam proton radiosurgery 3 mm set-up robustness		
		Clinical	Cochlear-optimized (study)	Nominal	VWmin	VWmax	Nominal	VWmin	VWmax
GTV	Dmean	13.7 (0.1)	13.7 (0.2)	12.6 (0.1)	12.2 (0.1)	12.9 (0.1)	12.6 (0.1)	12.2 (0.1)	12.8 (0.2)
	Dmedian	13.7 (0.2)	13.7 (0.2)	12.8 (0.2)	12.7 (0.2)	12.9 (0.2)	12.5 (0.1)	12.2 (0.1)	12.8 (0.2)
	$D_{98\%}$	12.1 (0.1)	12.1 (0.1)	12.2 (0.1)	11.9 (0.1)	12.2 (0.0)	12.2 (0.1)	11.9 (0.1)	12.4 (0.1)
	Dnear-max	14.9 (0.1)	14.9 (0.1)	14.0 (0.5)	13.8 (0.4)	14.1 (0.5)	13.2 (0.5)	12.6 (0.2)	13.3 (0.5)
	Dmax	15.0 (0.0)	15.0 (0.0)	14.2 (0.5)	14.0 (0.4)	14.3 (0.5)	13.6 (0.5)	12.7 (0.3)	13.5 (0.5)
	Dmin	11.0 (0.3)	10.9 (0.3)	11.6 (0.1)	11.3 (0.2)	11.7 (0.1)	12.1 (0.1)	11.3 (0.2)	12.3 (0.2)
	Paddick's Conformity Index	0.85 (0.05)	0.83 (0.05)	0.78 (0.05)	–	–	0.40 (0.05)	–	–
	Heterogeneity Index (median, IQR)	0.21 (0.20 – 0.21)	0.21 (0.20 – 0.21)	0.15 (0.14 – 0.16)	–	–	0.06 (0.05 – 0.09)	–	–
	Gradient Index (median, IQR)	4.5 (4.3 – 4.9)	4.6 (4.0 – 4.9)	5.7 (4.9 – 7.0)	–	–	4.5 (3.9 – 5.2)	–	–
Cochlea	Dmean (median, IQR)	9.8 (8.8 – 10.1)	**8.7 (6.1 – 9.5)** ($p < 0.001$)	9.9 (7.7 – 10.8) ($p = 0.97$)	9.1 (7.6 – 10.0)	10.1 (7.8 – 10.9)	**11.7 (10.4 – 11.9)** ($p = 0.001$)	9.8 (8.1 – 10.2)	12.0 (11.3 – 12.3)
	Dmedian (median, IQR)	9.8 (8.9 – 10.1)	8.8 (6.0 – 9.5)	9.9 (7.7 – 10.8)	9.2 (7.6 – 10.1)	10.1 (7.8 – 10.9)	11.8 (10.6 – 12.0)	9.9 (8.1 – 10.3)	12.0 (11.3 – 12.3)
	Dnear-max, (median, IQR)	10.6 (10.0 – 11.0)	9.8 (7.4 – 10.3)	10.8 (9.2 – 11.2)	10.2 (9.1 – 10.8)	10.9 (9.3 – 11.3)	12.1 (11.3 – 12.2)	10.7 (9.2 – 10.9)	12.3 (11.7 – 12.4)
	Dmax (median, IQR)	12.4 (11.6 – 12.8)	11.8 (9.9 – 12.1)	12.4 (11.2 – 12.6)	12.1 (11.1 – 12.4)	12.5 (11.2 – 12.6)	12.6 (12.2 – 12.7)	12.0 (11.3 – 12.2)	12.8 (12.5 – 12.9)
	Dmin	6.1 (1.7)	4.9 (2.4)	5.9 (2.7)	5.3 (2.3)	6.1 (2.8)	8.2 (2.6)	5.8 (2.3)	9.6 (2.2)
Brainstem	Dmean	2.6 (0.7)	2.5 (0.7)	1.7 (0.6)	1.6 (0.5)	1.9 (0.6)	2.6 (0.7)	1.8 (0.5)	3.6 (0.9)
	Dmedian	1.9 (0.6)	1.9 (0.7) $p = 0.48$	**0.2 (0.3)** $p < 0.001$	0.2 (0.2)	0.3 (0.4)	**0.7 (0.6)** $p < 0.001$	0.3 (0.3)	1.6 (1.0)
	Dnear-max	11.9 (0.3)	11.9 (0.3) $p = 0.43$	**12.1 (0.2)** $p = 0.001$	12.0 (0.2)	12.2 (0.2)	**12.4 (0.1)** $p < 0.001$	12.0 (0.2)	12.6 (0.1)
	Dmin	0.2 (0.1)	0.2 (0.1)	0	0	0	0	0	0
Isodose volume in cc	1 Gy, (median, IQR)	309 (257 – 438)	330 (234 – 406)	231 (194 – 251)	226 (190 – 245)	237 (200 – 258)	309 (265 – 335)	217 (188 – 244)	416 (356 – 440)
	2 Gy (median, IQR)	76 (62 – 108)	80 (60 – 106)	138 (105 – 155)	133 (102 – 150)	143 (110 – 161)	202 (165 – 220)	133 (99 – 147)	287 (240 – 314)
	3 Gy (median, IQR)	38 (31 – 54)	40 (31 – 51)	59 (41 – 80)	55 (38 – 74)	65 (45 – 88)	106 (77 – 130)	62 (47 – 82)	160 (115 – 192)
	4 Gy (median, IQR)	25 (20 – 35)	27 (20 – 33)	34 (27 – 44)	30 (24 – 39)	37 (30 – 49)	56 (43 – 68)	36 (27 – 44)	82 (65 – 99)
	6 Gy (median, IQR)	14 (11 – 20)	15 (11 – 19)	21 (17 – 25)	18 (15 – 25)	23 (19 – 31)	35 (28 – 42)	21 (16 – 27)	54 (43 – 63)
	8 Gy (median, IQR)	9 (7 – 13)	9 (7 – 12)	13 (11 – 19)	11 (9 – 16)	15 (12 – 21)	24 (19 – 30)	13 (10 – 18)	38 (30 – 46)
	10 Gy (median, IQR)	6 (4 – 9)	6 (4 – 8)	8 (7 – 12)	7 (6 – 11)	9 (7 – 13)	15 (12 – 21)	8 (6 – 12)	25 (20 – 32)
Trigeminal nerve	Dmean	5.5 (1.0)	5.3 (1.0) $p = 0.31$	5.9 (1.2) $p = 0.13$	4.8 (1.3)	6.9 (1.1)	**7.3 (1.2)** $p < 0.001$	4.9 (1.2)	9.3 (1.1)
	Dmedian	4.7 (1.3)	4.4 (1.4)	5.6 (2.1)	4.1 (2.1)	7.3 (1.6)	7.8 (2.5)	4.1 (1.9)	10.7 (1.4)
	Dnear-max	10.2 (1.3)	10.3 (1.3) $p = 0.55$	**11.1 (1.1)** $p = 0.02$	10.3 (1.8)	11.3 (0.8)	**12.1 (0.5)** $p < 0.001$	10.6 (1.4)	12.4 (0.3)

		Photon radiosurgery 0 mm PTV margin		Nine-beam proton radiosurgery 0 mm set-up robustness			Nine-beam proton radiosurgery 3 mm set-up robustness		
		Clinical	Cochlear-optimized (study)	Nominal	VWmin	VWmax	Nominal	VWmin	VWmax
GTV	Dmean	13.7 (0.1)	13.7 (0.1)	12.9 (0.2)	12.8 (0.2)	13.0 (0.2)	12.6 (0.1)	12.2 (0.1)	12.9 (0.1)
	Dmedian	13.7 (0.2)	13.7 (0.2)	12.9 (0.2)	12.8 (0.2)	13.0 (0.2)	12.6 (0.1)	12.2 (0.1)	12.8 (0.1)
	$D_{98\%}$	12.1 (0.1)	12.1 (0.1)	12.1 (0.1)	12.0 (0.1)	12.2 (0.1)	12.3 (0.0)	11.9 (0.0)	12.5 (0.0)
	Dnear-max	14.9 (0.1)	14.9 (0.1)	14.1 (0.5)	14.0 (0.4)	14.2 (0.4)	13.5 (0.5)	12.6 (0.3)	13.6 (0.5)
	Dmax	15.0 (0.0)	15.0 (0.0)	14.3 (0.5)	14.2 (0.5)	14.5 (0.5)	13.7 (0.6)	12.8 (0.4)	13.8 (0.5)
	Dmin	11.0 (0.3)	11.0 (0.3)	11.6 (0.1)	11.3 (0.1)	11.6 (0.1)	12.0 (0.1)	11.4 (0.1)	12.2 (0.1)
	Paddick's Conformity Index	0.85 (0.05)	0.83 (0.05)	0.82 (0.04)	–	–	0.44 (0.05)	–	–

(*continued on next page*)

Table 3 (*continued*)

		Photon radiosurgery 0 mm PTV margin		Nine-beam proton radiosurgery 0 mm set-up robustness			Nine-beam proton radiosurgery 3 mm set-up robustness		
		Clinical	Cochlear-optimized (study)	Nominal	VWmin	VWmax	Nominal	VWmin	VWmax
	Homogeneity Index (median, IQR)	0.21 (0.20 – 0.21)	0.21 (0.20 – 0.21)	0.15 (0.14 – 0.17)	–	–	0.09 (0.05 – 0.11)	–	–
	Gradient Index (median, IQR)	4.5 (4.3 – 4.9)	4.5 (4.3 – 4.9)	5.4 (4.6 – 6.8)	–	–	5.0 (4.1 – 5.6)	–	–
Cochlea	Dmean (median, IQR)	9.8 (8.8 – 10.1)	**8.7 (6.1 – 9.5)** (p <0.001)	9.5 (7.3 – 10.3) (p=0.41)	9.3 (7.2 – 9.9)	9.7 (7.5 – 10.4)	**11.5 (10.1 – 11.7)** (p=0.005)	10.1 (8.4 – 10.4)	11.8 (10.8 – 12.0)
	Dmedian (median, IQR)	9.8 (8.9 – 10.1)	8.8 (6.0 – 9.5)	9.5 (7.4 – 10.3)	9.2 (7.2 – 9.9)	9.7 (7.5 – 10.4)	11.5 (10.2 – 11.8)	10.1 (8.4 – 10.4)	11.8 (10.9 – 12.1)
	Dnear-max (median, IQR)	10.6 (10.0 – 11.0)	9.8 (7.4 – 10.3)	10.3 (8.9 – 10.9)	10.1 (8.6 – 10.6)	10.4 (9.0 – 11.0)	11.8 (10.9 – 12.0)	10.8 (9.5 – 10.9)	12.0 (11.4 – 12.2)
	Dmax (median, IQR)	12.4 (11.6 – 12.8)	11.8 (9.9 – 12.1)	12.3 (11.2 – 12.6)	12.1 (11.0 – 12.3)	12.4 (11.2 – 12.7)	12.4 (11.9 – 12.6)	11.9 (11.3 – 12.1)	12.6 (12.2 – 12.7)
	Dmin	6.1 (1.7)	4.9 (2.4)	5.4 (2.6)	5.2 (2.5)	5.5 (2.6)	8.3 (2.4)	6.4 (2.2)	9.4 (2.0)
Brainstem	Dmean	2.6 (0.7)	2.5 (0.7)	1.5 (0.5)	1.4 (0.5)	1.6 (0.6)	2.4 (0.7)	1.6 (0.5)	3.4 (0.9)
	Dmedian	1.9 (0.6)	1.9 (0.6) p=0.48	**0.2 (0.2)** p<0.001	0.2 (0.2)	0.3 (0.3)	**0.7 (0.5)** p<0.001	0.3 (0.2)	1.6 (1.0)
	Dnear-max	11.9 (0.3)	11.9 (0.3) p=0.43	**12.1 (0.3)** p=0.04	12.0 (0.3)	12.1 (0.2)	**12.4 (0.1)** p<0.001	11.9 (0.2)	12.5 (0.0)
	Dmin	0.2 (0.1)	0.2 (0.1)	0	0	0	0	0	0
Isodose volume in cc	1 Gy, (median, IQR)	309 (257–438)	330 (234 – 406)	150 (115 – 219)	143 (110 – 212)	159 (122 – 229)	260 (205 – 303)	158 (131 – 281)	384 (293 – 436)
	2 Gy (median, IQR)	76 (62 – 108)	80 (60 – 106)	52 (44 – 66)	48 (40 – 61)	58 (49 – 73)	81 (71 – 97)	56 (49 – 69)	113 (100 – 134)
	3 Gy (median, IQR)	38 (31 – 54)	40 (31 – 51)	36 (31 – 47)	32 (27 – 42)	40 (34 – 52)	58 (51 – 71)	38 (33 – 48)	84 (74 – 100)
	4 Gy (median, IQR)	25 (20 – 35)	27 (20 – 33)	28 (24 – 37)	25 (21 – 33)	31 (27 – 41)	46 (40 – 57)	29 (25 – 37)	68 (60 – 82)
	6 Gy (median, IQR)	14 (11 – 20)	15 (11 – 19)	18 (15 – 25)	16 (13 – 22)	21 (17 – 28)	46 (40 – 57)	29 (25 – 38)	68 (60 – 82)
	8 Gy (median, IQR)	9 (7 – 13)	9 (7 – 12)	12 (10 – 18)	10 (8 – 15)	14 (11 – 19)	22 (18 – 28)	13 (10 – 17)	35 (30 – 43)
	10 Gy (median, IQR)	6 (4 – 9)	6 (4 – 8)	8 (6 – 12)	6 (5 – 10)	8 (6 – 12)	15 (12 – 19)	8 (6 – 11)	24 (19 – 30)
Trigeminal nerve	Dmean	5.5 (1.0)	5.5 (1.0) p=0.31	5.8 (1.2) p=0.30	5.3 (1.1)	6.2 (1.2)	**7.8 (1.1)** p<0.001	5.8 (1.1)	9.3 (1.0)
	Dmedian	4.7 (1.3)	4.7 (1.3)	5.4 (1.8)	4.7 (1.6)	6.1 (1.8)	8.1 (1.7)	5.4 (1.6)	10.3 (1.2)
	Dnear-max	10.2 (1.3)	10.2 (1.3) p=0.55	10.8 (1.3) p=0.08	10.4 (1.5)	10.9 (1.2)	**12.1 (0.6)** p<0.001	10.8 (1.1)	12.3 (0.3)

Mean values (standard deviations) unless otherwise specified and indices of the different treatment plans. The bold numbers indicate a statistically significant difference compared to the **clinical photon plan**. The cochlear-optimized photon plans had significantly lower cochlear Dmean than the proton plans (Wilcoxon signed ranks test $p = 0.02$ for the 3-beam plan without set-up robustness; $p < 0.001$ for the proton plans with set-up robustness), with the exception of the nine-beam proton plan without set-up robustness ($p = 0.07$).

Abbreviations: Dnear-max = D_{35mm3}, Gy = Gray; in the case of proton therapy the Gray Relative Biological Effectiveness (RBE), IQR = inter-quartile range, PCI = Paddick's conformity index, VWmax = voxel-wise maximum error scenario, VWmin = voxel-wise minimum error scenario.

and for all isodose volumes compared to the nine-beam proton plans (up to a threshold of 0.8 Gy[RBE]). The photon plans, on the other hand, showed smaller volumes compared to the three-beam proton plans at all isodose values, with the exception of 1 Gy(RBE). With the addition of set-up robustness to the proton plans, all proton plans yielded a worse low-dose bath. Additional examples of treatment plans are shown in the Supplementary Materials (Supplementary Figure B.2).

4. Discussion

This study aimed to investigate whether the cochlear dose of clinical delivered vestibular schwannoma plans could be reduced by using either robotic photon radiosurgery or intensity-modulated proton therapy (IMPT). A cochlear dose reduction was achieved with cochlea-optimized photon radiosurgery plans without compromising tumor coverage or OAR constraints. This finding implies that the current clinical treatment planning protocol can be improved in favor of a more cochlear sparing strategy and possibly less risk of hearing loss. Patients with a greater distance between the tumor and the cochlea are especially good candidates for cochlea-sparing treatment; this insight could be used to select patients in clinical practice and is in line with previous studies that have reported better hearing outcomes in patients with a larger tumor to cochlea distance [10,34,35]. The cochlear dose decreases with approximately 1 Gy/Gy(RBE) per mm distance between the tumor and the cochlea.

Photon radiosurgery plans generally provided better cochlear sparing than proton therapy plans. Proton therapy with the current set-up robustness of 3 mm did not lower cochlear doses but could reduce the dose at a larger distance. Reducing the set-up robustness to 0 mm and using nine beam arrangements (compared to three) improved plan conformity and reduced OAR dose. However, in current clinical practice proton therapy is not able to improve the dose to structures closer to the tumor such as the cochlea, partly due to the currently used set-up robustness.

Although the cochlear dose in many patients could be reduced, the study's aim to reduce the overall mean cochlear dose by more than 1.5 Gy compared to the clinical photon plan, was not met. The average cochlear Dmean in this study (between 8.7 and 11.7) was higher than in several previous studies focusing specifically on minimizing hearing loss in vestibular schwannoma patients, which report dosages as low as 3 to 5 Gy. This may be due to the consecutive patient selection, in which 63 % of patients had a tumor that was directly adjacent to the cochlea, preventing the reduction of the cochlear dose. In comparison, another study found that 58 % of their patients had no tumor within the internal acoustic canal (IAC), resulting in better hearing outcomes post-radiosurgery [35]. In addition, other studies reported lower cochlear doses in photon radiosurgery than in the current study. This might be due to tumor coverage adjustments at the lateral segment of the tumor. In the current study, the decision was made not to compromise the tumor coverage as the primary treatment aim remains tumor control. Additionally, the objective was to have a Paddick's conformity index (PCI) of at least 0.77 (which is higher than several previous studies – although this is not always reported) [36]. Other factors of influence may be the prescribed isodose or the size (and the shape) of the tumor; this was not specifically examined in this study.

There is a lack of normal tissue complication probability (NTCP) models for hearing loss based on cochlear dose in vestibular schwannoma patients undergoing radiosurgery [11]. Previous photon

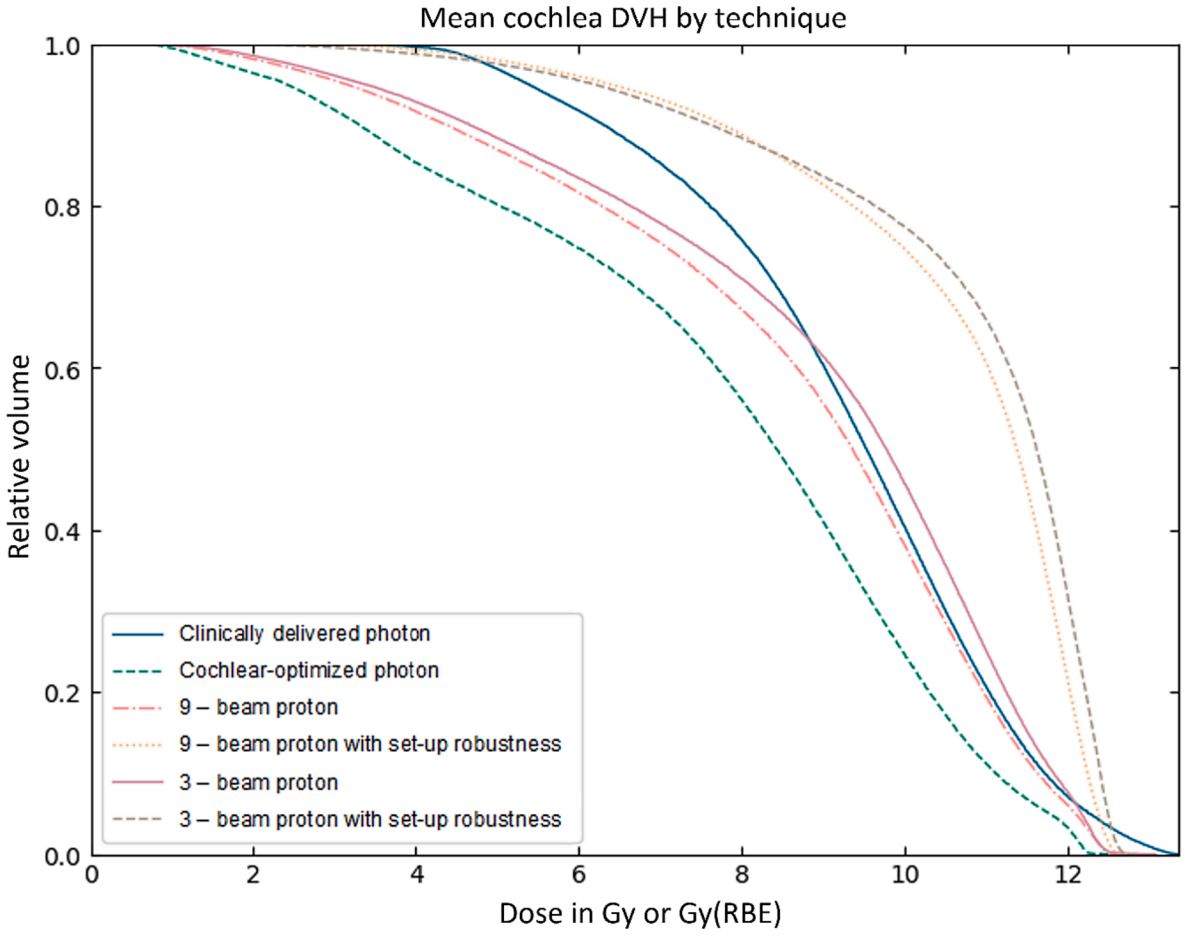

Fig. 1. Mean cochlea DVH by technique.

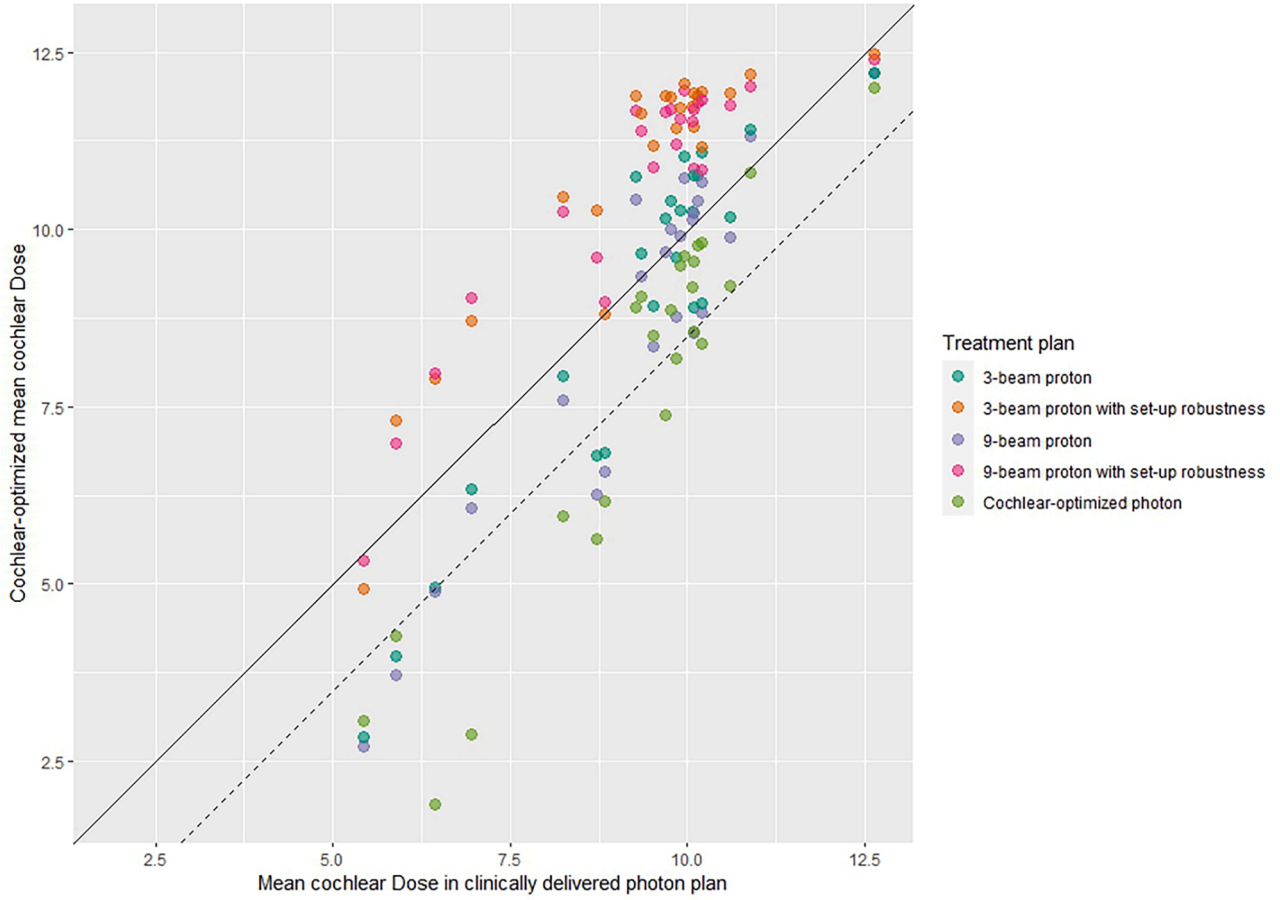

Fig. 2. The cochlear-optimized plans as a function of the cochlear Dmean of the clinical (photon) plan. Dashed line at the 1.5 Gy or Gy(RBE) reduction (study endpoint).

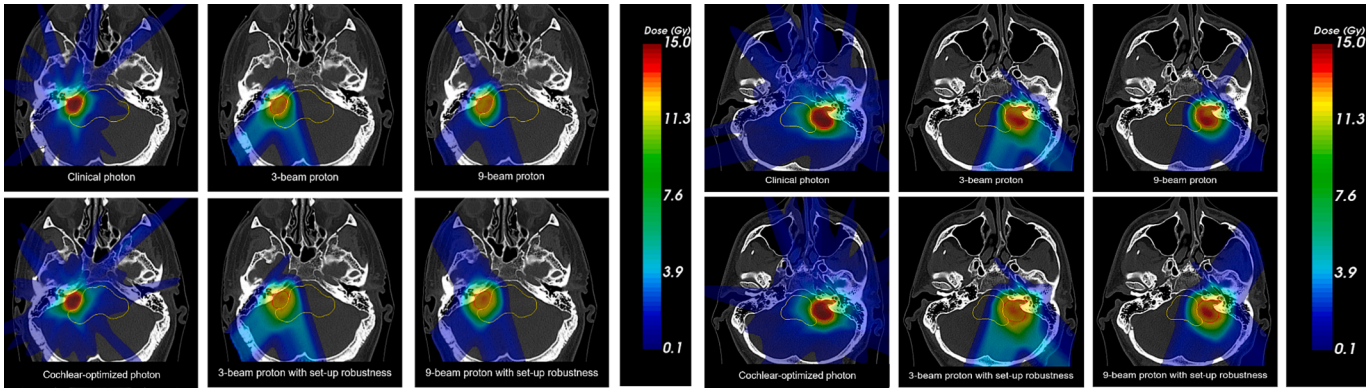

Fig. 3. Examples of six different treatment plans for one patient with a relatively long distance between the tumor and the cochlea (5 mm) and six different treatment plan of another patient with a tumor directly adjacent to the cochlea.

radiosurgery studies suggest that better hearing outcomes can be obtained by reducing the mean doses < 3–6 Gy, the maximum doses < 4–12 Gy, and minimum doses < 5–6 Gy [37,38]. No established gold standard for radiotherapy exists for vestibular schwannoma patients, and differences in local practices (i.e., patient selection) and endpoint definitions (Dmean, Dmin, Dmax, D90, V90, cochlear modiolus dose) make it difficult to compare different modalities [10,14,33]. Variations in treatment planning and delivery modalities between centers resulted in widely varying mean cochlear doses in a UK multicenter benchmark study, ranging from 3.1 to 12 Gy [39].

Thus far, only a few studies have focused on comparing the cochlear dose in vestibular schwannoma treatment plans – in photons only. One planning study - including very small tumors - compared LINAC-based to robotic radiosurgery (CyberKnife) and found a significant cochlear dosimetric superiority for CyberKnife with a mean cochlear dose of 5.4 vs 6.9 Gy for LINAC-based plans [18]. In another study, which compared GammaKnife, LINAC-based, and CyberKnife radiosurgery in relatively smaller vestibular schwannomas, LINAC provided the best conformity and GammaKnife the best gradient index [40]. The reported Paddick's conformity index is better in the current study than in several other studies: 0.78——0.85 in the current study versus 0.66——0.76 (all without utilizing treatment margins or set-up robustness) [37,40].

Compared to a previous study using a three-beam arrangement for vestibular schwannoma proton radiosurgery, this study reports higher cochlear doses [13,15]. This is likely due to differences in patient selection and treatment planning and delivery, such as the use of brass collimators that sharpen the lateral penumbra, a different beam angle through the temporal bone, a higher prescription isodose level of 90 %, and the inclusion of patients with smaller tumor volumes. The conformity index, however, was better in the current study (between 0.40 and 0.44 and 0.78–0.82 [with or without set-up robustness] compared to 0.29 [range 0.11–0.77] in the previous study), possibly in part due to the smaller tumor volumes. This study aimed to assess a possible reduction in cochlear dose with proton therapy by increasing the number and the angle of beam configurations. Compared to a three-beam configuration, nine-beam proton configurations improved the conformity index and reduced doses to organs at risk (except for the trigeminal nerve) and theoretically has the advantage of spreading distal end uncertainties. The improvement of the low-dose bath effect of proton therapy (versus photons) was less than expected, which was likely also a result of the beam angles going through the bilateral cerebellum. Additionally, beam angles were directed towards the cochlea to benefit patients with larger tumor to cochlea distances and to decrease dose to the brainstem (by limiting the distal end RBE uncertainties). However, this may have negatively impacted tumors adjacent to the cochlea (63 %). An assessment of the best beam angle configuration was beyond the scope of this study. Additionally, there remains ongoing debate regarding the RBE for proton therapy, which may be dependent on the specific localization of the beam.

Strengths of this study include the use of a robust automated treatment planning system for proton therapy, which allowed for a consistent generation of a large set of treatment plans and exploration of different methods. The patient population was reflective of clinical practice, and cochlear-optimized treatment plans were compared to the clinical treatment plans. However, limitations of this study include its restriction to patients with tumors extending to the cerebellopontine angle, omitting tumors with only intracanalicular component. Based on a previous study, 1.5 Gy was chosen as a cut-off value for the cochlear Dmean. This cut-off value enabled us to compare the results for each patient (and find subgroups), instead of looking at group averages that can be skewed by several data points. The chosen endpoint of 1.5 Gy, however, was only based on one study and its relevance for clinical practice, therefore, is yet uncertain. Additionally, collimators were not tested to sharpen the lateral penumbra of the fields and could improve the sparing of adjacent structures. This method is not yet available clinically for the proton therapy system used at HollandPTC. Furthermore, this is not a definite comparison, as vestibular schwannoma patients are also treated with other radiotherapy modalities that were not included in this study. Two patients were included who were postoperative. This reflects the clinical practice, but also increases the heterogeneity of the sample. Future studies could specifically focus on comparing different treatment modalities for patients with a larger tumor to cochlea distance, as these cases are the most likely to improve the cochlear dose.

In conclusion, a cochlear dose reduction is possible in some vestibular schwannoma radiosurgery plans while maintaining tumor coverage, especially when the tumor is not adjacent to the cochlea. Photon radiosurgery plans provided better cochlear sparing than proton radiosurgery plans with current set-up robustness.

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Credit authorship contribution statement

Kimberley S. Koetsier: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Visualization, Writing – original draft. **Michelle Oud:** Conceptualization, Data curation, Methodology, Investigation, Visualization, Writing – original draft. **Erik de Klerck:** Data curation, Investigation, Writing – review & editing. **Erik F Hensen:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Marco van Vulpen:** Conceptualization, Writing – review & editing. **Anne van Linge:** Conceptualization, Funding acquisition, Writing – review & editing. **Peter Paul van Benthem:** Supervision, Funding acquisition, Writing – review & editing. **Cleo Slagter:** Resources, Writing – review & editing. **Steven J.M. Habraken:** Conceptualization, Methodology, Writing – review & editing. **Mischa S. Hoogeman:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft. **Alejandra Méndez Romero:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Resources, Writing – original draft.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Dr. Hoogeman reports grants from Varian Medical Systems Particle Therapy GmbH & Co. KG, Troisdorf, Germany, during the conduct of the study; membership of advisory board Accuray, Sunnyvale, USA and participant/presenter Accuray Thinktank Meeting, outside the submitted work; and The Department of Radiotherapy (Erasmus Medical Center Cancer Institute, The Netherlands) has research collaborations with Elekta AB, Stockholm, Sweden, Accuray Inc., Sunnyvale, CA, USA, Varian, Palo Alto, CA, USA, RaySearch Laboratories, Stockholm, Sweden, outside the submitted work].

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Appendix A. Supplementary data

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