Supplementary material for Stokkevåg et al., Normal tissue complication probability models in plan evaluation of children with brain tumors referred to proton therapy

Table S1. Overview of patient population and prescribed doses.

#	Diagnosis	Tumor location	Age	Prescription dose Gy / Gy(RBE)
1	PNET	Right temporal lobe	1	54 (30x1.8)
2	PNET	Midline, 3rd ventricle	2	54 (30x1.8)
3	PNET	Left temporal lobe	4	54 (30x1.8)
4	PNET	Parietal/occipital lobe	3	50.4 (28x1.8)
5	PNET (medulloblastoma)	Posterior fossa	11	54 (13x1.8;CSI/17x1.8;boost)
6	PNET (medulloblastoma)	Posterior fossa	4	54 (13x1.8;CSI/17x1.8;boost)
7	PNET (medulloblastoma)	Posterior fossa	15	54 (13x1.8;CSI/17x1.8;boost)
8	PNET (medulloblastoma)	Posterior fossa	7	54 (13x1.8;CSI/17x1.8;boost)
9	PNET (medulloblastoma)	Posterior fossa	15	54 (13x1.8;CSI/17x1.8;boost)
10	PNET (supratentorial)	Central, midline	16	54 (20x1.8;CSI/10x1.8;boost)
11	PNET (medulloblastoma)	Posterior fossa	5	54 (13x1.8;CSI/17x1.8;boost)
12	PNET (medulloblastoma)	Posterior fossa	16	54 (13x1.8;CSI/17x1.8;boost)
13	Ependymoma	Supratentorial, parietal lobe	2	54 (30x1.8)
14	Ependymoma	Cerebrum, parietal/occipital lobe	8	54 (30x1.8)
15	Ependymoma	Infratentorial	2	54 (30x1.8)
16	Ependymoma	Infratentorial	3	54 (30x1.8)
17	Ependymoma	Infratentorial	3	59.4 (33x1.8)
18	Ependymoma	Supratentorial, frontal lobe	4	54 (30x1.8)
19	Ependymoma	Infratentorial	2	54 (30x1.8)
20	Ependymoma	Infratentorial	2	54 (30x1.8)
21	ATRT	Cerebellum	4	50.4 (28x1.8)
22	ATRT	Cerebellum, pineal gland, central	3	50.4 (28x1.8)
23	ATRT	Cerebellum	1	50.4 (28x1.8)
24	ATRT	Cerebellum, brainstem	2	54 (30x1.8)
25	Rhabdomyosarcoma	Left mastoid, intracranial extension	4	50.4 (28x1.8)
26	Rhabdomyosarcoma	Right mastoid, sinuses	12	41.4 (23x1.8)
27	Rhabdomyosarcoma	Left sinuses	11	54 (30x1.8)
28	Rhabdomyosarcoma	Nasopharynx, oral cavity	16	50.4 (28x1.8)
29	Pilocytic astrocytoma	Cerebellum, brainstem	17	54 (30x1.8)
30	Pilocytic astrocytoma	Posterior hypothalamus	15	54 (30x1.8)
31	Germinoma	Midline, thalamus	15	54 (30x1.8)
32	Germinoma	Midline, hypothalamus	12	54 (30x1.8)
33	Chondrosarchoma	Medulla, brainstem, skull base	14	72(36x2)
34	Craniopharygioma	Midline	8	50.4 (28x1.8)
35	Ganglioglioma	Right temporal lobe	10	54 (30x1.8)
36	Low grade glioma	Cerebellum	10	50.4 (28x1.8)
37	Neurocytoma	Central, lateral ventricles	6	59.4 (33x1.8)
38	Yolk-sac tumor	Midline, thalamus	17	54 (30x1.8)
39	Head and neck	Right parotid gland	16	66 (33x2)
40	Head and neck	Right gingiva	12	59.4 (33x1.8)

PNET = primitive neuroectodermal tumor

ATRT = atypical teratoid rhabdoid tumor

Table S2. Dose/volume dependencies and thresholds. Normal tissue complication probability models.

ENDPOINT/COMPLICATION	Structure	Dose/vol. dependency	Ped-spec	Reference
Growth hormone deficiency (GHD)				
50% risk at 5 years	Hypothalamus	Dmean >16 Gy	yes	Merchant 2011
80-100% risk of GHD at 5 years	Pituitary gland	Dmean >30 Gy	yes	Scoccianti 2015; Darzy 2009
NTCP GHD at 5 years	Hypothalamus	Dmean	yes	Merchant 2011
Neurocognitive impairment				
IQ decline	Temporal lobes	Dmean	yes	Redmond 2013
IQ decline	Hippocampi	Dmean	yes	Redmond 2013
Memory impairment	Left temporal lobe	Dmean	yes	Armstrong 2010
Delayed verbal and visual memory	Left hippocampus	V20Gy	yes	Zureick 2018
>10% decline in full-scale IQ	Left temporal lobe	V43Gy >13%	yes	Jalali 2010
NTCP IQ decline	Supratentorial brain	V20, V30, V55	yes	Merchant 2006
Auditory toxicity				
Risk of grade 3+ hearing loss	Cochlea	Dmean >35 Gy	yes	Paulino 2010; Scoccianti 2015
20% risk of grade 2+ tinnitus	Cochlea	Dmean >30 Gy	no	Lee 2015
NTCP tinnitus	Cochlea	Dmean	no	Lee 2015
Visual impairment				
Risk of rad-induced optic neuropathy	Optic nerves	Dmax >54 Gy	no*	Mayo 2010; Moiseenko 2011
Risk of rad-induced optic neuropathy	Optic chiasm	Dmax >54 Gy	no*	Mayo 2010; Moiseenko 2011
NTCP rad-induced optic neuropathy	Optic chiasm	DVH	no*	Burman/Emami 1991
Xerostomia				
Risk of saliva flow <25% of pre-treatment	Parotid glands	Dmean >20 Gy	no	Moiseenko 2012
NTCP xerostomia	Least irradiated gland	Dmean	no	Houweling 2010
Excess absolute risk of secondary cancers				
Radiation-induced carcinoma	Brain	DVH (OED)	yes	Schneider 2011
Radiation-induced carcinoma	Parotid glands	DVH (OED)	yes	Schneider 2011

*No diff. reported between adults and paediatric patients

Table S3. Overview of dose/volume metrics across all patients and number of patients/organs below indicated pediatric tolerance dose thresholds.

STRUCTURE / Dose-volume metric	Median (range)		Patients/organs below dose threshold	
	Proton	**VMAT**	**Proton**	**VMAT**
Endocrine structures				
Hypothalamus / Dmean [Gy(RBE)/Gy]*	16.6 (0-54.0)	19.1 (0-54.3)	18 (47%)	18 (47%)
Pituitary / Dmean [Gy(RBE)/Gy]*	9.1 (0.0-61.2)	24.8 (0.6-59.1)	25 (66%)	22 (58%)
Cognitive structures				
Temporal lobes / Dmean [Gy(RBE)/Gy]*	10.1 (0.0-39.8)	14.0 (0.4-41.5)	-	-
Hippocampi / Dmean [Gy(RBE)/Gy]*	20.7 (0.0-53.3)	21.0 (0.3-52.4)	-	-
Left temporal lobe / Dmean [Gy(RBE)/Gy]*	12.2 (0.0-39.8)	17.4 (0.3-41.5)	-	-
Left temporal lobe / V43Gy [%]	2.6 (0.0-24.7)	1.7 (0.0-61.8)	29 (76%)	31 (82%)
Left hippocampus / V20Gy [%]*	22.1 (0.0-51.2)	27.5 (0.3-52.4)	-	-
Supratentorial brain / V20Gy [%]*	9.8 (0-100)	12.3 (0-100)	-	-
Supratentorial brain / V30Gy [%]	5.8 (0-100)	6.4 (0-100)	-	-
Supratentorial brain / V55Gy [%]	0.0 (0.0-15.6)	0.0 (0.0-16.4)	-	-
Brainstem / Dmean [Gy(RBE)/Gy]*	23.9 (0.0-53.2)	28.5 (0.9-53.5)	-	-
Brainstem / D10% [Gy(RBE)/Gy]*	51.4 (0.0-55.2)	51.6 (1.7-56.0)	-	-
Audio structures				
Cochlea (# of structures) Dmean [Gy(RBE)/Gy]*	2.2 (0-70.9)	17.7 (0.3-72.3)	62 (82%)	55 (72%)
Ocular structures				
Optic nerves and chiasm Dmean [Gy(RBE)/Gy]*	1.4 (0.0-55.4)	20.5 (0.4-54.0)	-	-
Optic nerves and chiasm Dmax [Gy(RBE)/Gy]*	9.5 (0.0-57.6)	24.8 (0.7-64.4)	106 (93%)	106 (93%)
Salivary gland structures				
Parotid glands / least irradiated gland Dmean [Gy(RBE)/Gy]*	0.0 (0.0-65.6)	8.8 (0.1-66.3)	61 (80%) / 36 (95%)	58 (76%) / 34 (89%)

* Statistically significant difference in dose metric by Wilcoxon signed rank test

Table S4. Estimated risk of complications excluding CSI patients.

Estimated risk excl. CSI patients	**Median risk (range)**	
ENDPOINT	**Proton**	**VMAT**
Growth hormone deficiency*	7.2 (0-94) %	11.3 (0-97) %
Cognitive decline* (IQ points)	1.8 (0.0-18.9)	2.4 (0.0-21.3)
Tinnitus* (# of cochleas)	0.2 (0-93) %	1.9 (0-94) %
Optic neuropathy*	0.0 (0-15) %	0.0 (0-5) %
Xerostomia*	0.6 (1-9) %	1.4 (1-11) %
Radiation-induced brain carcinoma*	6.2 (0-12) %	7.9 (0-19) %
Radiation-induced parotid carcinoma*	0.1 (0-3) %	2.6 (0-6) %

* Statistically significant difference in dose metric by Wilcoxon signed rank test

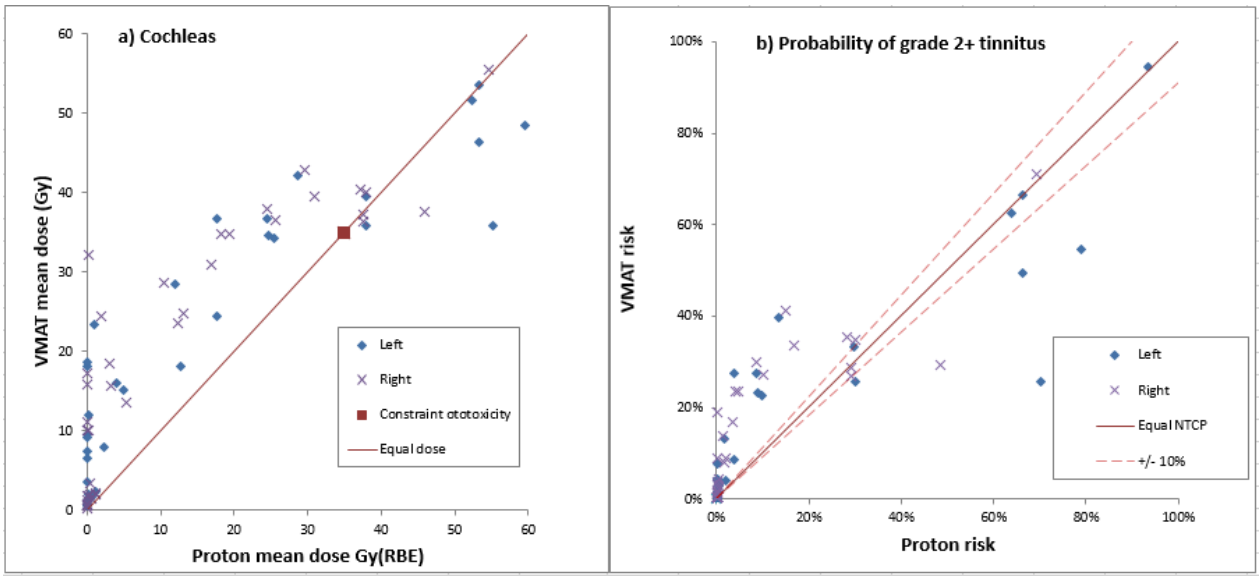

Figure S1. Cochlear mean doses per patient compared for VMAT and PT plans. Pediatric dose threshold indicated. b) Estimated probability of tinnitus per patient. Equal dose and risk indicated by solid line, +/-10% relative difference in risk indicated by dashed line.

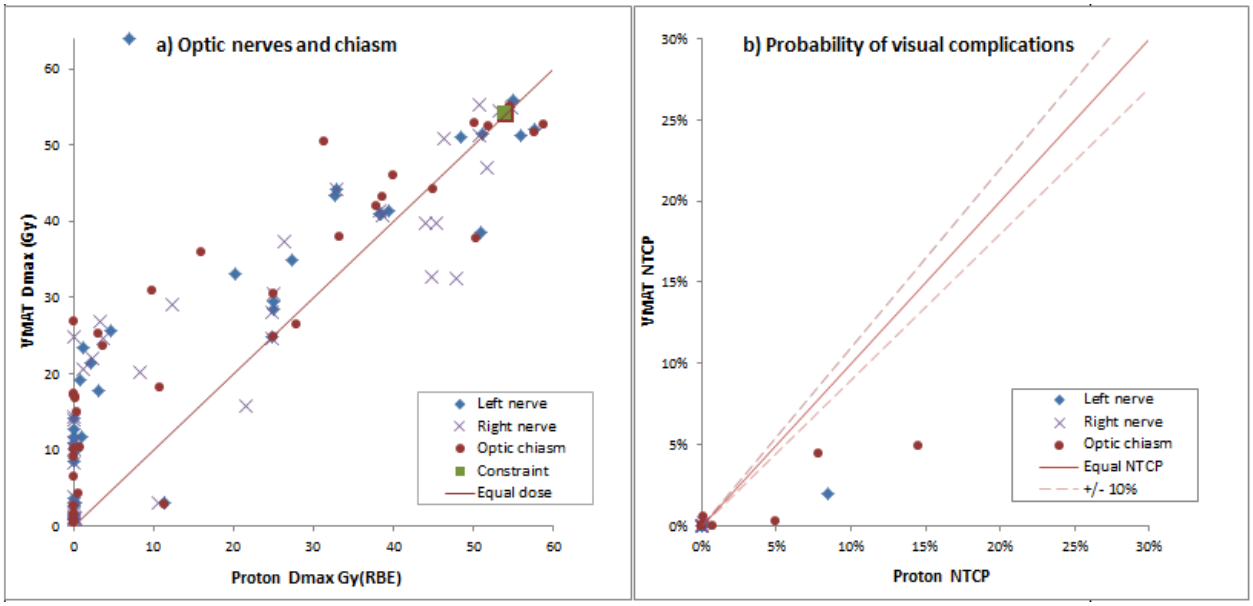

Figure S2. a) Maximum doses to optical structures compared for the VMAT and PT. Dose threshold at 54 Gy indicated, exceeded with both modalities for patient #18 and #37, exceeded in VMAT only for #1 and #33, and PT only for #16-17. b) Estimated probability of complication per patient. Equal dose and risk indicated by solid line, +/-10% relative difference in risk indicated by dashed line.

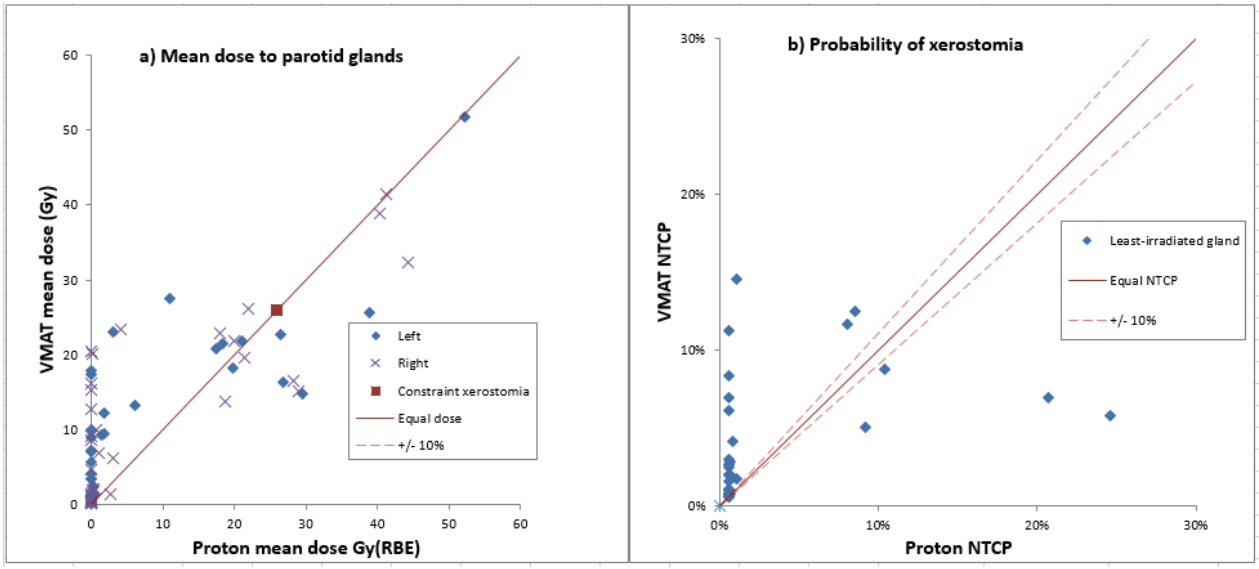

Figure S3. a) Mean dose to parotid glands compared for VMAT and proton plans. Pediatric dose threshold to maintain risk of xerostomia low indicated. b) Estimated risk of xerostomia per patient. Equal dose and risk indicated by solid line, +/-10% relative difference in risk indicated by dashed line.

#	Diagnosis	GHD	Cognitive decline	Audio L	Audio R	Optic toxicity	Xerostomia	SC brain	SC parotid glands
1	PNET	P	P	P	C	C	P	C	P
2	PNET	P	P	C	C	C	C	P	C
3	PNET	P	P	C	C	C	C	P	C
4	PNET	C	P	C	C	C	C	C	C
5	PNET (medulloblastoma)	X	C	P	P	C	P	C	C
6	PNET (medulloblastoma)	C	C	P	P	C	P	C	X
7	PNET (medulloblastoma)	X	C	P	P	C	P	C	P
8	PNET (medulloblastoma)	X	C	P	P	C	X	C	C
9	PNET (medulloblastoma)	C	C	P	P	C	X	C	P
10	PNET (medulloblastoma)	C	X	X	C	C	X	C	P
13	Ependymoma	P	P	C	C	C	C	P	C
14	Ependymoma	C	P	C	C	C	C	P	C
15	Ependymoma	X	P	X	P	C	P	X	P
16	Ependymoma	X	P	X	P	X	P	P	P
17	Ependymoma	X	X	X	P	X	P	X	P
18	Ependymoma	P	P	C	C	X	C	P	C
19	Ependymoma	C	C	P	P	C	P	C	P
20	Ependymoma	C	C	P	P	C	P	X	P
21	ATRT	C	C	P	P	C	P	C	P
22	ATRT	P	P	P	P	C	C	P	P
23	ATRT	P	P	P	P	C	P	C	P
24	ATRT	C	P	C	P	P	P	P	P
25	Rhabdomyosarcoma	C	C	C	P	C	P	P	P
26	Rhabdomyosarcoma	P	P	C	P	C	P	P	P
27	Rhabdomyosarcoma	P	C	P	P	C	P	P	P
28	Rhabdomyosarcoma	C	C	C	C	C	X	C	C
29	Pilocytic astrocytoma	P	P	P	P	C	C	P	P
30	Pilocytic astrocytoma	C	P	C	C	C	C	P	C
31	Germinoma	P	P	C	C	C	C	P	C
32	Germinoma	C	P	C	C	P	C	P	C
33	Chondrosarchoma	P	X	C	P	C	P	P	P
34	Craniopharygioma	C	C	P	P	C	P	P	P
35	Ganglioglioma	C	X	C	X	C	C	P	C
36	Low grade glioma	X	C	P	P	C	P	X	P
37	Neurocytoma	C	P	P	P	P	C	P	P
38	Yolk-sac tumor	P	P	C	C	C	C	P	C
39	Tumour in ear gland	P	C	P	C	C	P	P	P
40	Gingival tumor	C	C	C	C	C	P	P	P

P	Protons superior
C	Comparable within +-10% with cutoff <1% / <1 IQ point
X	VMAT superior

Figure S4. Overview of estimated relative differences in risk for each patient across the investigated endpoints. Difference in estimated risk exceeding ±10% with lower cutoff at 1% risk (or 1 IQ point in the case of cognitive decline) is here defined as superior of the opposite technique. PNET = primitive neuroectodermal tumor. ATRT = atypical teratoid rhabdoid tumor.

#	Diagnosis	GHD	Cognitive decline*	Audio L	Audio R	Optic toxicity	Xerostomia	SC brain	SC parotid glands
1	PNET	5 %	0.4	4 %	2 %	0 %	1 %	0 %	3 %
2	PNET	26 %	0.7	0 %	0 %	0 %	0 %	3 %	0 %
3	PNET	2 %	2.6	0 %	0 %	0 %	0 %	5 %	0 %
4	PNET	3 %	1.7	1 %	0 %	0 %	0 %	1 %	1 %
5	PNET (medulloblastoma)	-2 %	0.1	19 %	21 %	0 %	4 %	0 %	0 %
6	PNET (medulloblastoma)	-4 %	0.3	13 %	17 %	0 %	4 %	0 %	-1 %
7	PNET (medulloblastoma)	-19 %	-0.4	26 %	26 %	0 %	14 %	1 %	1 %
8	PNET (medulloblastoma)	-7 %	0.3	14 %	17 %	0 %	-2 %	0 %	0 %
9	PNET (medulloblastoma)	-4 %	0.0	3 %	5 %	0 %	-14 %	0 %	1 %
10	PNET (medulloblastoma)	4 %	-2.1	-4 %	-2 %	0 %	-19 %	0 %	1 %
13	Ependymoma	5 %	7.0	0 %	0 %	0 %	0 %	7 %	1 %
14	Ependymoma	4 %	2.2	0 %	0 %	0 %	0 %	5 %	0 %
15	Ependymoma	-32 %	0.4	-17 %	12 %	-1 %	11 %	-2 %	2 %
16	Ependymoma	-6 %	0.3	-45 %	19 %	-10 %	2 %	2 %	3 %
17	Ependymoma	-40 %	-0.5	-24 %	19 %	-5 %	2 %	-3 %	4 %
18	Ependymoma	21 %	3.2	0 %	0 %	-3 %	0 %	5 %	1 %
19	Ependymoma	0 %	0.0	4 %	1 %	0 %	6 %	0 %	5 %
20	Ependymoma	0 %	-0.3	2 %	2 %	0 %	1 %	-1 %	4 %
21	ATRT	0 %	0.0	3 %	1 %	0 %	0 %	0 %	3 %
22	ATRT	19 %	1.6	1 %	2 %	0 %	0 %	2 %	2 %
23	ATRT	2 %	0.9	7 %	8 %	0 %	2 %	0 %	6 %
24	ATRT	6 %	1.5	0 %	13 %	4 %	1 %	4 %	1 %
25	Rhabdomyosarcoma	1 %	0.0	-1 %	3 %	0 %	6 %	1 %	2 %
26	Rhabdomyosarcoma	9 %	1.9	1 %	6 %	0 %	1 %	7 %	2 %
27	Rhabdomyosarcoma	2 %	0.0	1 %	1 %	0 %	1 %	1 %	3 %
28	Rhabdomyosarcoma	0 %	0.0	0 %	0 %	0 %	-4 %	0 %	0 %
29	Pilocytic astrocytoma	25 %	3.6	5 %	7 %	0 %	0 %	3 %	1 %
30	Pilocytic astrocytoma	-1 %	3.4	0 %	0 %	0 %	0 %	3 %	0 %
31	Germinoma	10 %	3.1	0 %	0 %	0 %	0 %	3 %	0 %
32	Germinoma	2 %	4.1	0 %	0 %	2 %	0 %	4 %	0 %
33	Chondrosarchoma	2 %	-1.1	1 %	3 %	0 %	2 %	2 %	2 %
34	Craniopharygioma	0 %	0.2	12 %	7 %	0 %	3 %	2 %	2 %
35	Ganglioglioma	1 %	-0.2	0 %	-19 %	0 %	0 %	1 %	0 %
36	Low grade glioma	-4 %	-0.1	24 %	19 %	0 %	8 %	-2 %	3 %
37	Neurocytoma	6 %	2.4	2 %	4 %	2 %	0 %	4 %	1 %
38	Yolk-sac tumor	41 %	1.8	0 %	0 %	0 %	0 %	3 %	0 %
39	Tumour in ear gland	1 %	0.3	1 %	-1 %	0 %	2 %	2 %	2 %
40	Gingival tumor	0 %	0.0	0 %	0 %	0 %	1 %	0 %	2 %

ΔNTCP ≥ 5% in favour of protons
ΔNTCP ≥ 5% in favour of VMAT
*In case of cognitive decline ΔNTCP bounderies are set to ±5 IQ points

Figure S5. Overview of estimated risk difference for each patient across the investigated endpoints. Difference in NTCP percentage points and IQ points (VMAT-PT). PNET = primitive neuroectodermal tumor. ATRT = atypical teratoid rhabdoid tumor. SC = secondary cancer. For patient #16 there was a compromise in target coverage for both VMAT and PT.

Supplementary methods

Growth hormone deficiency was estimated according to hypothalamus and pituitary gland dose [8, 11] using criteria of peak growth hormone levels < 3 ng/mL at five years post treatment [33]. Neurocognitive function was estimated on the basis of dose/volume effects for the supratentorial brain, temporal lobes, and hippocampi [7, 34, 35]. Probability of memory impairment was modeled based on mean dose to the left temporal lobe [6] and decline in IQ points was estimated based on supratentorial brain dose/volumes [5]. Ototoxicity was estimated based on cochlear dose. Pediatric dose thresholds for sensorineural hearing loss was taken from Paulino et al. [11, 12], whereas a Lyman Kutcher Burman (LKB) mean dose volume model derived from an adult population were used to estimate risk of tinnitus with parameters TD50 = 46.5 Gy and m=0.35 [13, 14]. Risk of visual impairment was estimated using dose to the optic nerves and chiasm [14]. For these optic structures, no difference has been reported between adult and pediatric populations [11] and thereby an LKB adult volume-based model was employed with parameters: TD50=65 Gy, m=0.14 and n=0.25 [36, 37]. To evaluate the risk of xerostomia, available adult-based criteria and model estimates were used; the QUANTEC criteria of at least one parotid gland with mean dose <20 Gy [15] and the preferred LKB (mean dose) model with parameters TD50 = 39.9 Gy, m=0.4 [38]. Excess absolute risk (EAR) of radiation-induced carcinoma was estimated using DVH data with the best fit model, equation 7 from Schneider et al. [39], describing the excess absolute risk of secondary cancer (carcinoma) of the brain and salivary glands and assuming attained age of 80 years.

Citations numbered as in main document