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Original Research Article

Treatment plan comparison of proton vs photon radiotherapy for lower-grade gliomas

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ABSTRACT

Background and purpose: Patients with lower-grade gliomas are long-term survivors after radiotherapy and may benefit from the reduced dose to normal tissue achievable with proton therapy. Here, we aimed to quantify differences in dose to the uninvolved brain and contralateral hippocampus and compare the risk of radiation-induced secondary cancer for photon and proton plans for lower-grade glioma patients.

Materials and methods: Twenty-three patients were included in this in-silico planning comparative study and had photon and proton plans calculated (50.4 Gy(RBE = 1.1), 28 Fx) applying similar dose constraints to the target and organs at risk. Automatically calculated photon plans were generated with a 3 mm margin from clinical target volume (CTV) to planning target volume. Manual proton plans were generated using robust optimisation on the CTV. Dose metrics of organs at risk were compared using population mean dose-volume histograms and Wilcoxon signed-rank test. Secondary cancer risk per 10,000 persons per year (PPY) was estimated using dose-volume data and a risk model for secondary cancer induction.

Results: CTV coverage (V95%>98%) was similar for the two treatment modalities. Mean dose (D_{mean}) to the uninvolved brain was significantly reduced from 21.5 Gy (median, IQR 17.1–24.4 Gy) with photons compared to 10.3 Gy(RBE) (8.1–13.9 Gy(RBE)) with protons. D_{mean} to the contralateral hippocampus was significantly reduced from 6.5 Gy (5.4–11.7 Gy) with photons to 1.5 Gy(RBE) (0.4–6.8 Gy(RBE)) with protons. The estimated secondary cancer risk was reduced from 6.7 PPY (median, range 3.3–10.4 PPY) with photons to 3.0 PPY (1.3–7.5 PPY) with protons.

Conclusion: A significant reduction in mean dose to uninvolved brain and contralateral hippocampus was found with proton planning. The estimated secondary cancer risk was reduced with proton therapy.

1. Introduction

The number of centres offering proton therapy (PT) increases rapidly worldwide. The fundamental properties of proton beams allow a reduction in dose to normal tissue compared to treatment with photons [1]. Adult patients with a range of brain tumours are candidates for PT due to the potential reduction of the degree of radiation-induced brain injuries, and positive impact on patients' quality of life [2]. There is, however, no general consensus on the recommendation of PT for patients with lower-grade gliomas (LGG). A direct dosimetric comparison

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of 'state-of-the-art' photon treatment to PT will be of value to guide the radiation oncologists to which patients may benefit from one treatment modality over the other.

Previous studies on adult patients with brain cancer have reported on the dose advantages with PT compared to different photon therapy techniques; Harrabi et al. found dose reductions when comparing 3D conformal RT (3D-CRT) to PT [3]. Eekers et al. reported on a multicentre planning study comparing several photon techniques to proton treatment for 25 LGG patients and concluded that PT could especially spare dose to contralateral organs [4]. Dutz et al. also reported lower doses to brain organs at risk (OARs) for a heterogenous cohort of 92 brain cancer patients treated with PT when compared to volumetric modulated arc therapy (VMAT) plans and found that 87% of these patients would have been selected for PT if a model-based approach had been used [5].

In particular, patients with LGGs may benefit from dose reduction of the normal tissue in the brain since their median survival is often more than 10 years after radiotherapy [6–8] and hence radiation-induced late effects can have extensive consequences for these patients. Our knowledge of the dose–response relationship in the brain is limited, and it is, therefore, difficult to determine who will benefit most from PT. Some normal tissue complication probability (NTCP) models for prediction of side effects of radiotherapy are available, including radiation necrosis, vision impairment and hearing loss [9–11]. LGG patients will, however, often be treated with low prescription doses and the above-mentioned side effects will not be as relevant as e.g. neurocognitive impairment and fatigue. There exist only a few follow-up studies on cognitive changes after radiotherapy of LGG patients [12–16], hence there is some debate on the shape of the dose–response curve. It is hypothesised that dose to the hippocampi will result in some neurocognitive decline due to its link to neurogenesis [17], and the degree of dose reduction achievable with PT is important to study. In the Netherlands, a model-based approach is used as a selection tool [18] and interestingly, the Dutch referral for proton therapy for LGG patients with a good prognosis also includes a 5% dose reduction to both hippocampi minus the clinical target volume (CTV) as eligibility criterion [19].

Another aspect to consider when selecting patients for either photon or proton treatment is the risk of secondary cancer (SC) following radiotherapy. Data on SC in the brain originates mainly from paediatric cohorts treated with cranial radiotherapy, where excess odds ratios (EOR) of 0.33 and 0.079 per Gy have been reported for gliomas and 1.06 and 5.1 per Gy for non-malignant and malignant meningiomas by the North American and British Cancer Survivor Study respectively [20]. Different photon techniques have been shown to have a theoretical impact on the risk of secondary tumours [21]. The rapid distal dose fall-off of protons may significantly reduce the integral dose and thus reduce the risk of SC. Quantifying the consequence of potential dose reduction on the risk of radiation-induced SC may be an important tool in the selection of radiotherapy treatment modality. In a previous study by Dennis et al. the risk of SC was estimated for 11 LGG patients treated with passively scattered PT and compared to intensity modulated radiation therapy (IMRT) plans [12]. Here, the risk of SC was estimated to be twice as high with IMRT compared to PT. The SC risk has, however, been shown to be increased with IMRT compared to both other photon therapy techniques and PT [22].

The primary aim of this study was therefore to quantify the potential dose reduction to the uninvolved brain and contralateral hippocampus with PT compared to automatically generated state-of-the-art photon plans. Our secondary aim was to estimate the potential risk reduction of secondary cancer as a result of the dose reduction which can be achieved with PT.

2. Materials and methods

In this in-silico planning comparative study, automatically generated photon therapy plans were compared to manually calculated PT plans.

Table 1
Patient characteristics.

Characteristics	n	%
Total patients	23	100
Male	18	78
Female	5	22
Age (years)		
Mean (range)	45	(22–77)
Diagnose		
Diffuse Astrocytoma	14	61
Oligodendroglioma	3	13
Anaplastic Astrocytoma	4	17
Pilocytic Astrocytoma	2	9
Clinical Target Volume (cm^3)		
Median (range)	238	(175–296)
Surgery		
Biopsy	10	44
Partial resection	9	39
Complete resection	4	17
Laterality		
Left	16	70
Right	6	26
Midline	1	4
Location		
Frontal lobe	7	30
Temporal lobe	6	26
Parietal lobe	9	39
Cerebellum	1	4
Performance Status (WHO)		
0	10	43
1	11	48
2	2	9

2.1. Patients

A historical cohort of patients treated with photon therapy for low-grade gliomas from 2013 to 2018 in one of four radiotherapy clinics in Denmark was available for this study. From this cohort, we randomly selected 24 patients treated at Aarhus University Hospital. The study was approved by the Danish patient safety authority (3-3013-2680/1). Patient and tumour characteristics are displayed in Table 1.

2.2. Target and organ at risk delineations

Clinically used delineations of target volumes and OARswere available for this study. Delineations were performed on the treatment planning CT images (3 mm slice thickness) fused with T1 and T2 weighted pre- and postoperative MRI sequences (1 mm slice thickness). National guidelines for target and OAR delineation and treatment planning were used [23]. The original clinically defined gross tumour volume (GTV) and CTV were used without modifications. The GTV was defined as the hyper-intense tumour volume on the T2 weighted fluid attenuated inversion recovery (FLAIR) magnetic resonance images including the contrast enhanced tumour and resection cavity (if present). The CTV was obtained by adding an isotropic margin of 1 cm to the GTV and adjusting to anatomical barriers. An experienced radiation oncologist (YL-R) checked and adjusted delineations of OARs to ensure that all delineated structures adhered to Danish national guidelines. Delineated OARs were brain, brainstem, chiasm, cochlea, eyes, hippocampi, lenses, optic nerves, optic tracts, pituitary and spinal cord [23,24]. Uninvolved brain was defined as the entire brain volume, excluding CTV and brainstem (brain-CTV-BS). In cases where the CTV included the left or right hippocampus (20 out of 46), the hippocampus was still delineated as a separate volume. For two patients this was not possible and only one hippocampus was delineated.

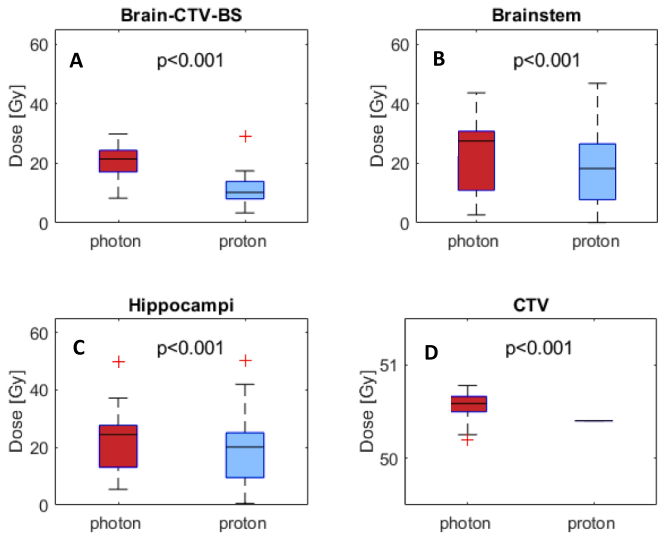

Fig. 1. Box plots of the mean dose to the uninvolved brain (Brain-CTV-BS) (A), brainstem (B), hippocampi (C) and CTV (D) for photon plans (red) and proton plans (blue). Outliers are marked with a red plus sign. A significant reduction is observed for all of these structures with proton therapy compared to photon therapy. CTV coverage was obtained with both treatment modalities. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.3. Treatment planning

To ensure that all treatment plans were optimised according to current clinical guidelines and using the updated OARs segmentations, new plans were calculated for all patients. The prescribed dose was 50.4 Gy in 28 fractions for all patients. The OAR dose constraints were the same for photon and proton plans and followed national guidelines (suppl. Table S1 and S2). One patient was excluded from analysis due to the tumour location overlapping with the spinal cord. The overlap resulted in a volume of the target where the prescription dose could not be reached.

All photon treatment plans were generated by one treatment planner (CRH) with Pinnacle Autoplan (Philips Healthcare, Eindhoven, The Netherlands) [25]. The treatment technique was typically a full VMAT arc with a collimator angle of 15 degrees. Few patients had only a partial arc if the tumour location was very lateral. The dose grid spacing was 3x3x3 mm^3 and control point spacing was 2 degrees. The Autoplan treatment technique that was used is detailed in suppl. table S2. The planning target volume (PTV) was defined as CTV + 3 mm isocentric margin and 98% of the target volume was covered by at least 95% of the dose. After Autoplan optimisation, manual fine-tuning optimisation was performed to adhere to the national guidelines for target and critical OARs.

All proton treatment plans were generated by a second treatment planner (CSB) according to clinical practice in Eclipse TPS v13.7 (Varian Medical Systems, Inc., Palo Alto, CA, USA). A fixed relative biological effect (RBE) of 1.1 was used in the optimisation of all proton plans. All proton doses reported were thus corrected for this RBE. We used three fields with a minimum angular separation of 30 degrees. In cases where robust CTV coverage could not be obtained with three fields, we used four (with the same minimum separation). Any titanium clips were avoided when choosing field directions. Furthermore, distal edges ending in critical OARs were avoided where possible. Plans were calculated using robust optimisation to the CTV and serial organs if they were close to the target volume. Fourteen scenarios were calculated with an isocenter shift of 0 mm or ± 3 mm in the x, y and z direction combined with a range uncertainty of 3.5%. All plans were normalised to the CTV mean and optimised to cover 98% of the target volume with at least 95% of the dose. The dose grid spacing was 1x1x1 mm^3. Target coverage was evaluated for both the nominal plan and the worst-case scenario. All plans were reviewed by an experienced clinical physicist (JFK).

2.4. Organ at risk dose volume histogram analysis

Dose-volume histograms (DVHs) for the uninvolved brain, brainstem, chiasm, hippocampi, optic tracts and pituitary gland were extracted using Eclipse Scripting Application Programming Interface from the TPS and population data were analysed in MATLAB using an in-house developed script. The population mean DVHs were calculated by averaging the individual patient DVHs within each dose bin. The population DVH variation was calculated similarly.

2.5. Secondary cancer risk

The risk of developing an SC in the brain after radiotherapy was calculated according to the method proposed by Schneider et al. [26] and is described in detail in the supplementary material A. Briefly, the uninvolved brain DVH was used in combination with a dose–response model to calculate the SC risk as excess absolute risk (EAR) per 10,000 persons per year (PPY).

2.6. Statistical methods

A paired Wilcoxon signed-rank test was used to test for differences between photon and proton plans with p-values less than 0.05 considered significant. For the population mean DVHs there was no correction for multiple testing and the individual dose bins were considered dependent. A p-value for each dose bin was calculated for the paired photon and proton mean DVHs and plotted along these as a curve. This p-value curve should only be used as an illustration to indicate dose ranges with a significant difference.

The treatment planning study was planned and conducted according to the RATING guidelines [27]. The authors have evaluated the study and found a RATING score of 97%.

3. Results

Clinically satisfactory target coverage (PTV for photon therapy plans and CTV for PT plans, V95% >98%) was obtained for all patients (N = 23) and there was no significant difference between the two treatment modalities. Doses to all delineated OARs in both photon and proton plans met protocol constraints (suppl. tables S1 and S2). Photon plans had a significantly higher mean dose (D_{mean}) to the uninvolved brain with a median D_{mean} of 21.5 Gy (17.1–24.4 Gy, IQR) compared to proton plans demonstrating a median D_{mean} of 10.3 Gy(RBE) (8.1–13.9 Gy

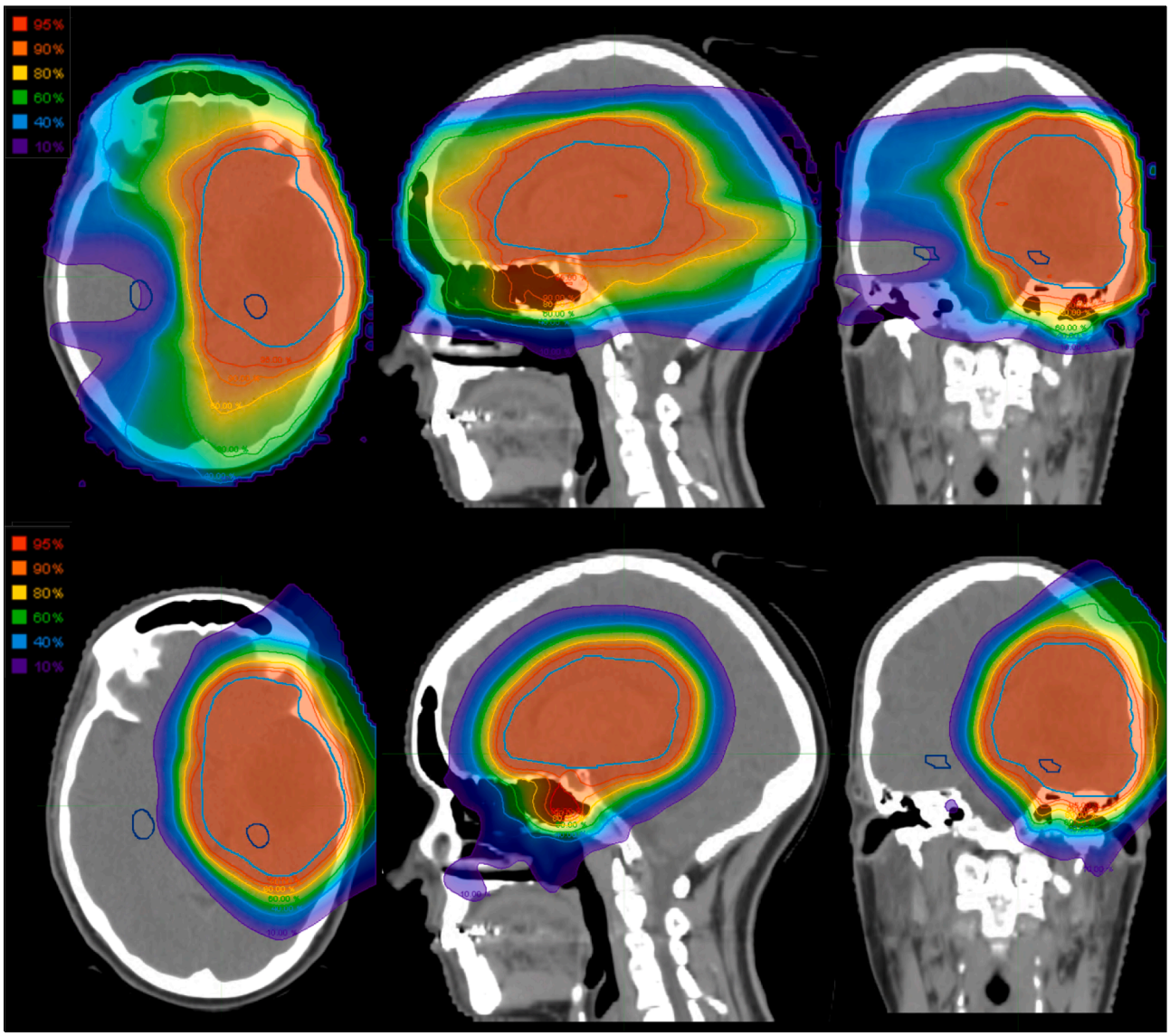

Fig. 2. Example patient with a photon (A) and proton (B) dose distributions on the planning CT scan. Both dose washes show the 30–95% of the prescription dose range, CTV in cyan and hippocampi in dark blue. The low dose volume is clearly reduced in the proton plan and it is evident from (A) that sparing of the contralateral hippocampus may result in higher doses to the surrounding normal tissue with photon therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(RBE), $p < 0.0001$, Fig. 1, Table 2). An illustrative example of treatment plans from the two different modalities is displayed in Fig. 2. A similar dose reduction was observed for the brainstem D_{mean}, with a reduction from 27.5 Gy (11.0–30.8 Gy) with photons to 18.2 Gy(RBE) (7.8–26.6 Gy(RBE) with protons ($p < 0.001$). A significant reduction was observed for the bilateral hippocampi with a median D_{mean} of 24.5 Gy (13.1–27.7 Gy) with photons compared to 20.1 Gy(RBE) (9.5–25.2 Gy(RBE) with protons ($p < 0.001$, Fig. 3) as well as for ipsi- and contralateral hippocampus alone, supplementary Fig. S1. Median D_{mean} to the contralateral hippocampus was 6.5 Gy (5.4–11.7 Gy) with photons compared to 1.5 Gy(RBE) (0.4–6.8 Gy(RBE)) with protons ($p < 0.001$). The individual proton D_{mean} for uninvolved brain and both ipsi- and contralateral hippocampus was in the majority of cases lower than the photon D_{mean} (Fig. 4). Doses to the remaining OARs were not significantly lower with PT compared to photon therapy (Figs. S1-S4), and were even slightly higher in some cases (Table 2).

The estimated secondary cancer risk was significantly reduced for proton plans with a median EAR of 3.0 per 10,000 persons per year (PPY) (range 1.3–7.5 per 10,000 PPY) compared to photon plans with a median EAR of 6.7 per 10,000 PPY (range 3.3–10.4 per 10,000 PPY), $p < 0.0001$ (Suppl. Material Fig. S5).

4. Discussion

In this study, we have shown that the mean dose to hippocampi and uninvolved brain can be significantly reduced with PT compared to automatically optimised state-of-the-art photon treatment plans. Also, we found a significant decrease in the estimated risk of SC using PT compared to photon therapy with a theoretical model for calculation of the risk of SC induction in the brain after radiotherapy.

The potential clinical benefit of the lower doses to tissue surrounding the target volumes remains to be confirmed in clinical studies [9]. PT is particularly advantageous with regards to sparing contralateral tissue, however, also ipsilateral structures are important to spare and may result in a larger overall NTCP difference as was shown in the paper by Dutz et al. [5]. In their in-silico study 87% of a cohort of 92 patients could have been referred to PT if $\Delta NTCP > 10\%$ for a given complication when comparing PT to photon therapy. For 51 (55%) of their patients,

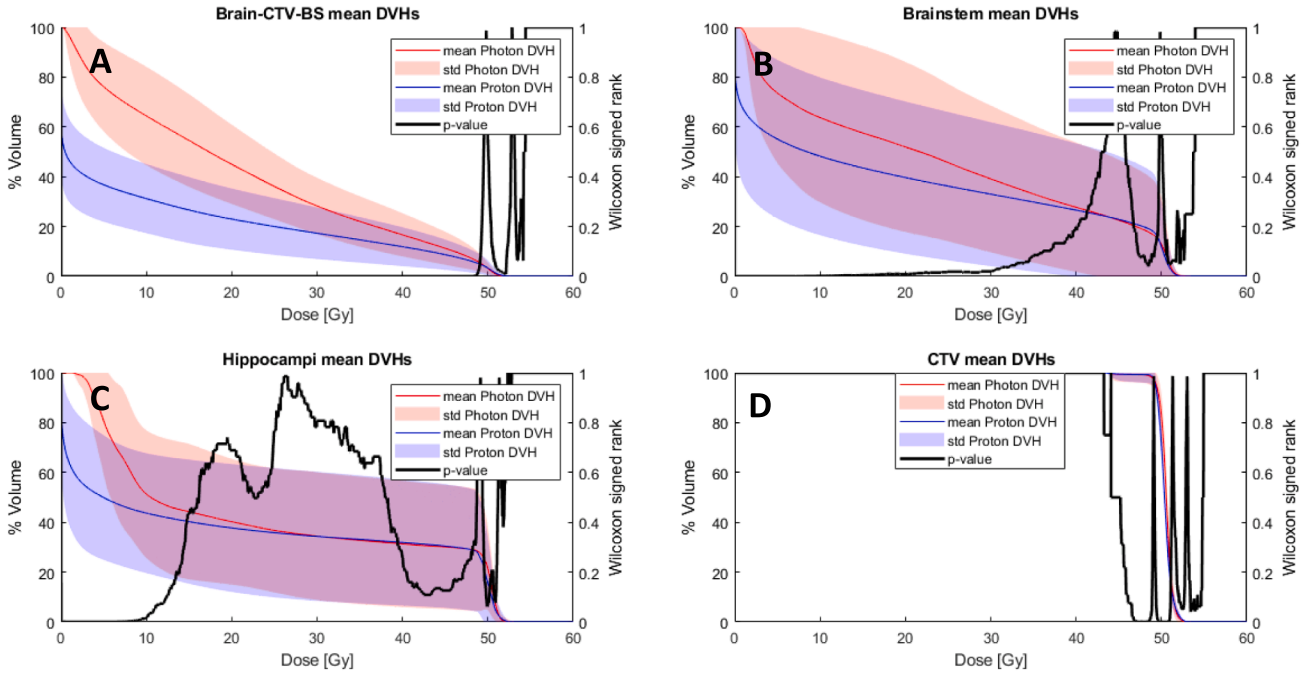

Fig. 3. Mean DVHs for the uninvolved brain (Brain-CTV-BS) (A), brainstem (B), hippocampi (C) and CTV (D) for photon (red) and proton plans (blue). A significant dose reduction to brain and brainstem (A, B) is obtained with proton therapy, for hippocampi the reduction is significant below 10 Gy. CTV coverage is similar with both modalities although minor differences are observed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

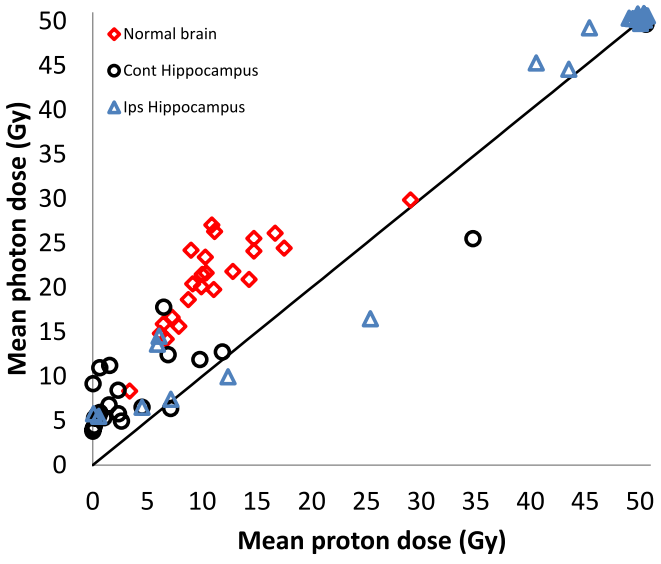

Fig. 4. Mean photon dose (y-axis) to the uninvolved brain (red diamonds), contra- (black circles) and ipsilateral (blue triangles) hippocampus versus mean proton dose (x-axis) for all patients. The black line is the identity line. For all patients, a photon plan results in a higher mean dose to the uninvolved brain. For two patients, the ipsilateral hippocampus receives 3 and 9 Gy more with the proton plan and for another patient, the contralateral hippocampus receives 9 Gy more with the proton plan. In all three cases, doses to the OARs are well below the dose limits and possibly could have been reduced upon further optimisation of the plans. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the change in NTCP arose from the model on delayed recall from Gondi et al. [28]. If we apply this model to our patients, 7 of 23 patients (30%) would have a ΔNTCP > 10%. The model is, however, based on a wide range of radiation schemes and a more heterogenous cohort of 18 brain cancer patients. The dose–response relationship in this model could not be confirmed in an independent study by Haldbo-Classen et al. on a more homogeneous population of LGG patients [29] nor in the study by Jaspers et al. [30]. The potential cognitive benefit of a given dose reduction is therefore likely overestimated by Dutz et al. since the observed complication rates are lower than those predicted by Gondi et al. [28].

All photon therapy plans in this study were generated automatically whereas the PT plans were generated manually. A fairer comparison would be to calculate both types of plans using automated planning which was not available for PT at our institution at the time of this planning study. Both types of treatment plans do, however, follow national guidelines and two independent treatment planners performed all optimisations blinded to each other. This is also why the dose to some OARs may have had more focus in one plan compared to the other. In both cases, treatment plans have been calculated as would have been the case in routine clinical practice. Treatment planning for PT is still in the early stages and there is room for improvement when it comes to e.g. finding the optimal field angles, robustness optimisation and evaluation, multifield vs. single-field optimisation, optimal range shifter usage and considerations on linear energy transfer and distal edge [31–35].

The RBE of protons is not a constant equal to 1.1 but varies with e.g. linear energy transfer, dose and biological effect [31]. It would therefore be of interest to recalculate the proton plans taking a variable RBE into account. The constant value of 1.1 is, however, commonly used clinically in PT planning, and therefore also chosen in this study, since we aimed to compare clinically relevant treatment plans. The potential higher RBE at the distal end of the proton beam was indirectly considered in this study by avoiding OARs close to the distal edge of one or more fields. Another important aspect to discuss is the comparison of

Table 2
Dose metrics for normal tissue. Median mean, maximum and interquartile range doses to OARs for all patients. The maximum dose is the dose to 0.027 cm^3. BS is the brainstem.

	Dose metric	Photon		Proton		Wilcoxon signed rank test
		Median	IQR	Median	IQR	
Brain-CTV-BS	Mean [Gy]	21.5	17.1–24.4	10.3	8.1–13.9	**p < 0.001**
	Max [Gy]	53.2	52.8–53.8	53.2	52.7–53.5	p = 0.52
Brainstem	Mean [Gy]	27.5	11.0–30.8	18.2	7.8–26.6	**p < 0.001**
	Max [Gy]	52.0	50.6–52.5	51.6	50.7–52.2	p = 0.25
Chiasm	Mean [Gy]	30.6	10.9–44.3	34.4	6.4–46.4	p = 0.22
	Max [Gy]	44.9	15.0–49.9	49.5	16.4–50.9	p = 0.32
Pituitary	Mean [Gy]	19.0	6.4–28.0	27.6	5.8–35.6	p = 0.88
	Max [Gy]	34.8	9.6–39.5	36.8	10.8–46.5	p = 0.08
Hippocampi	Mean [Gy]	24.5	13.1–27.7	20.1	9.5–25.2	**p < 0.001**
	Max [Gy]	51.9	51.5–52.0	51.4	50.2–52.3	p = 0.96
Hippocampus Ipsilateral	Mean [Gy]	49.8	13.8–50.4	49.0	8.4–50.3	**p = 0.01**
	Max [Gy]	51.8	47.2–52.0	51.5	50.3–52.2	p = 0.69
Hippocampus Contralateral	Mean [Gy]	6.5	5.4–11.7	1.5	0.4–6.8	**p < 0.001**
	Max [Gy]	22.5	14.2–39.2	20.8	7.4–43.1	p = 0.18
Optic Tract Ipsilateral	Mean [Gy]	48.6	18.6–49.9	49.5	10.8–50.4	p = 0.90
	Max [Gy]	50.3	24.7–51.2	50.9	24.1–51.5	p = 0.90
Optic Tract Contralateral	Mean [Gy]	36.3	12.0–40.1	32.4	1.9–40.0	**p = 0.007**
	Max [Gy]	43.2	13.8–47.0	44.2	6.0–48.4	p = 0.76
Optic Nerve Ipsilateral	Mean [Gy]	20.1	6.4–35.8	19.0	6.0–41.2	p = 0.13
	Max [Gy]	35.2	14.3–49.0	48.5	23.4–50.2	**p = 0.03**
Optic Nerve Contralateral	Mean [Gy]	12.0	3.5–19.7	1.1	0.05–7.7	**p < 0.001**
	Max [Gy]	15.3	7.2–39.5	14.4	1.8–40.7	p = 0.43

photon vs. proton treatments: Photon plans are optimised to cover a PTV whereas in PT planning, coverage is obtained for the CTV and combined with robust optimisation. This has been up for much debate, still, the PTV concept is being used clinically for photon treatments and hence this is what was done in this study and presumably will be so for quite some time.

Dennis et al. also reported on lower doses to OARs with PT and a two-fold increase (from 47 to 106 per 10,000 PPY) in the estimated risk of radiation-induced SC with IMRT treatment plans compared to the delivered passively scattered PT plans for a small cohort of 11 patients with LGG [12]. In their study, the dose to the whole brain (including the CTV) was used for the calculation and resulted in a higher absolute risk of secondary cancer. There may be considerable uncertainties associated with the absolute values of these calculations, however when performing relative comparisons these uncertainties are in the range of 2-5% [36]. Even with significant uncertainties, it is important to estimate the risk as this can give an impression of the magnitude of the risk and what the relative risk reduction is, which will have a lower uncertainty.

We have only calculated the risk of SC induction in the brain and not for the entire body. The clinical effect of the low doses which will inevitably be present during a radiotherapy treatment course is not well-known. However, Brenner et al. found an increased risk of SC after radiotherapy treatment compared to surgery alone in prostate cancer patients [37]. Grantzau et al. reported similar results in breast cancer patients [38], whereas a study by Wiltink et al. showed no difference in the risk of SC for a pooled cohort of patients with rectal or endometrial cancer who were randomly allocated to either treatment with or without RT [39]. The use of passively scattered PT results in higher neutron doses to the patients compared to active scanning [40]. How photon therapy and the resulting neutron production relates to these PT techniques is still of some debate [41] although there seems to be agreement that active scanning reduces neutron doses compared to both photon and passive scattered PT. Scattered neutron dose is known to be highly biologically effective and of great concern in the potential induction of secondary cancer. Emerging epidemiological studies of passively scattered protons have not shown an increased risk of secondary cancer [42,43]. The concern of secondary cancer may not apply to all LGG patients but may be relevant to consider in selected groups of patients, especially those with an expectation of long-term survival [44].

In conclusion, this in-silico study showed that proton therapy can significantly reduce doses to the uninvolved brain and contralateral hippocampus when compared to photon therapy for lower-grade glioma patients. Our work shows that for these patients specifically, proton therapy has a potential to spare cognition and prevent radiation-induced secondary cancer.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This work was funded by the Danish Cancer Society, grant no. R-204-A12365, DCCC Radiotherapy - The Danish National Research Center for Radiotherapy, and DCCC - Danish Comprehensive Cancer Center. The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2021.11.008.

References

[1] Brada M, Pijls-Johannesma M, de Ruysscher D. Current clinical evidence for proton therapy. Cancer J. 2009;15:319–24. https://doi.org/10.1097/PPO.0b013e3181b6127c.
[2] Weber DC, Lim PS, Tran S, Walser M, Bolsi A, Kliebsch U, et al. Proton therapy for brain tumours in the area of evidence-based medicine. Br. J. Radiol. 2020;93:20190237. https://doi.org/10.1259/bjr.20190237.
[3] Harrabi SB, Bougatf N, Mohr A, Haberer T, Herfarth K, Combs SE, et al. Dosimetric advantages of proton therapy over conventional radiotherapy with photons in young patients and adults with low-grade gliomaDosimetrische Vorteile der Protonentherapie gegenüber der konventionellen Strahlentherapie mit Photonen

bei jungen Patienten und Erwachsenen mit niedriggradigem Gliom. Strahlenther Onkol. 2016;192:759–69. https://doi.org/10.1007/s00066-016-1005-9.
[4] Eekers DBP, Roelofs E, Cubillos-Mesías M, Niël C, Smeenk RJ, Hoeben A, et al. Intensity-modulated proton therapy decreases dose to organs at risk in low-grade glioma patients: results of a multicentric in silico ROCOCO trial. Acta Oncol. 2019; 58:57–65. https://doi.org/10.1080/0284186X.2018.1529424.
[5] Dutz A, Lühr A, Troost EGC, Agolli L, Bütof R, Valentini C, et al. Identification of patient benefit from proton beam therapy in brain tumour patients based on dosimetric and NTCP analyses. Radiother. Oncol. 2021;160:69–77. https://doi.org/10.1016/j.radonc.2021.04.008.
[6] Shaw EG, Scheithauer BW, O'Fallon JR. Management of supratentorial low-grade gliomas. Oncology 1993;7:97–104. https://doi.org/10.1016/0360-3016(93)90602-r.
[7] Olson JD, Riedel E, DeAngelis LM. Long-term outcome of low-grade oligodendroglioma and mixed glioma. Neurology 2000;54:1442–8. https://doi.org/10.1212/WNL.54.7.1442.
[8] Pignatti F, van den Bent M, Curran D, Debruyne C, Sylvester R, Therasse P, et al. Prognostic factors for survival in adult patients with cerebral low-grade glioma. J. Clin. Oncol. 2002;20:2076–84. https://doi.org/10.1200/JCO.2002.08.121.
[9] Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constine LS, Eisbruch A, et al. Use of normal tissue complication probability models in the clinic. Int. J. Radiat. Oncol. Biol. Phys. 2010;76:S10–9. https://doi.org/10.1016/j.ijrobp.2009.07.1754.
[10] Mayo C, Martel MK, Marks LB, Flickinger J, Nam J, Kirkpatrick J. Radiation dose-volume effects of optic nerves and chiasm. Int. J. Radiat. Oncol. Biol. Phys. 2010; 76:S28–35. https://doi.org/10.1016/j.ijrobp.2009.07.1753.
[11] Lee T-F, Yeh S-A, Chao P-J, Chang L, Chiu C-L, Ting H-M, et al. Normal tissue complication probability modeling for cochlea constraints to avoid causing tinnitus after head-and-neck intensity-modulated radiation therapy. Radiat. Oncol. 2015; 10. https://doi.org/10.1186/s13014-015-0501-x.
[12] Dennis ER, Bussière MR, Niemierko A, Lu MW, Fullerton BC, Loeffler JS, et al. A comparison of critical structure dose and toxicity risks in patients with low grade gliomas treated with IMRT versus proton radiation therapy. Technol. Cancer Res. Treat. 2013;12:1–9. https://doi.org/10.7785/tcrt.2012.500276.
[13] Sherman JC, Colvin MK, Mancuso SM, Batchelor TT, Oh KS, Loeffler JS, et al. Neurocognitive effects of proton radiation therapy in adults with low-grade glioma. J. Neuro-Oncol. 2016;126:157–64. https://doi.org/10.1007/s11060-015-1952-5.
[14] Shih HA, Sherman JC, Nachtigall LB, Colvin MK, Fullerton BC, Daartz J, et al. Proton therapy for low-grade gliomas: Results from a prospective trial. Cancer 2015;121:1712–9. https://doi.org/10.1002/cncr.29237.
[15] Thurin E, Nyström PW, Smits A, Werlenius K, Bäck A, Liljegren A, et al. Proton therapy for low-grade gliomas in adults: A systematic review. Clin. Neurol. Neurosurg. 2018;174:233–8. https://doi.org/10.1016/j.clineuro.2018.08.003.
[16] T.A. Lawrie, D. Gillespie, T. Dowswell, J. Evans, S. Erridge, L. Vale, et al. Long-term neurocognitive and other side effects of radiotherapy, with or without chemotherapy, for glioma. Cochrane Database Syst. Rev. (2019) CD013047. https://doi.org/10.1002/14651858.CD013047.pub2.
[17] Moreno-Jiménez EP, Flor-García M, Terreros-Roncal J, Rábano A, Cafini F, Pallas-Bazarra N, et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat. Med. 2019;25:554–60. https://doi.org/10.1038/s41591-019-0375-9.
[18] Langendijk JA, Lambin P, De Ruysscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: The model-based approach. Radiother. Oncol. 2013;107:267–73. https://doi.org/10.1016/j.radonc.2013.05.007.
[19] van der Weide HL, Kramer MCA, Scandurra D, Eekers DBP, Klaver YLB, Wiggenraad RGJ, et al. Proton therapy for selected low grade glioma patients in the Netherlands. Radiother. Oncol. 2021;154:283–90. https://doi.org/10.1016/j.radonc.2020.11.004.
[20] Turcotte LM, Neglia JP, Reulen RC, Ronckers CM, van Leeuwen FE, Morton LM, et al. Risk, risk factors, and surveillance of subsequent malignant neoplasms in survivors of childhood cancer: A review. J. Clin. Oncol. 2018;36:2145–52. https://doi.org/10.1200/JCO.2017.76.7764.
[21] Treutwein M, Steger F, Loeschel R, Koelbl O, Dobler B. The influence of radiotherapy techniques on the plan quality and on the risk of secondary tumors in patients with pituitary adenoma. BMC Cancer 2020;20:88. https://doi.org/10.1186/s12885-020-6535-y.
[22] Schneider U, Lomax A, Pemler P, Besserer J, Ross D, Lombriser N, et al. The impact of IMRT and proton radiotherapy on secondary cancer incidence. Strahlenther. Onkol. 2006;182:647–52. https://doi.org/10.1007/s00066-006-1534-8.
[23] Danish Neuro Oncology Group. Retningslinjer for strålebehandling 2016. http://www.dnog.dk/assets/files/Retningslinier PDF/DNOG 2016 Retningslinjer for straalebehandling final.pdf (accessed July 8, 2021).
[24] Scoccianti S, Detti B, Gadda D, Greto D, Furfaro I, Meacci F, et al. Organs at risk in the brain and their dose-constraints in adults and in children: A radiation oncologist's guide for delineation in everyday practice. Radiother. Oncol. 2015; 114:230–8. https://doi.org/10.1016/j.radonc.2015.01.016.
[25] Hansen CR, Bertelsen A, Hazell I, Zukauskaite R, Gyldenkerne N, Johansen J, et al. Automatic treatment planning improves the clinical quality of head and neck cancer treatment plans. Clin. Transl. Radiat. Oncol. 2016;1:2–8. https://doi.org/10.1016/j.ctro.2016.08.001.
[26] U. Schneider, M. Sumila, J. Robotka, Site-specific dose-response relationships for cancer induction from the combined Japanese A-bomb and Hodgkin cohorts for doses relevant to radiotherapy. Theor. Biol. Med. Model. 8 (2011) Article number 27. https://doi.org/10.1186/1742-4682-8-27.
[27] Hansen CR, Crijns W, Hussein M, Rossi L, Gallego P, Verbakel W, et al. Radiotherapy Treatment plannINg study Guidelines (RATING): A framework for setting up and reporting on scientific treatment planning studies. Radiother. Oncol. 2020;153:67–78. https://doi.org/10.1016/j.radonc.2020.09.033.
[28] Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int. J. Radiat. Oncol. Biol. Physics 2013;85:348–54. https://doi.org/10.1016/j.ijrobp.2012.11.031.
[29] Haldbo-Classen L, Amidi A, Lukacova S, Wu LM, Oettingen GV, Lassen-Ramshad Y, et al. Cognitive impairment following radiation to hippocampus and other brain structures in adults with primary brain tumours. Radiother. Oncol. 2020;148:1–7. https://doi.org/10.1016/j.radonc.2020.03.023.
[30] J. Jaspers, A. Mèndez Romero, M.S. Hoogeman, M. van den Bent, R.G.J. Wiggenraad, M.J.B. Taphoorn, et al. Evaluation of the hippocampal normal tissue complication model in a prospective cohort of low grade glioma patients—an analysis within the EORTC 22033 clinical trial. Front. Oncol. 9 (2019) Article 991. https://doi.org/10.3389/fonc.2019.00991.
[31] Paganetti H. Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer. Phys. Med. Biol. 2014;59:R419–72. https://doi.org/10.1088/0031-9155/59/22/R419.
[32] J. Unkelbach, M. Alber, M. Bangert, R. Bokrantz, T.C.Y. Chan, J.O. Deasy, A. Fredriksson, B.L. Gorissen, M. van Herk, W. Liu, H. Mahmoudzadeh, O. Nohadani, J.V. Siebers, M. Witte, H.X. Robust radiotherapy planning. Phys. Med. Biol. 63 (2018) 22TR02. https://doi.org/10.1088/1361-6560/AAE659.
[33] Casares-Magaz O, Toftegaard J, Muren LP, Kallehauge JF, Bassler N, Poulsen PR, et al. A method for selection of beam angles robust to intra-fractional motion in proton therapy of lung cancer. Acta Oncol. 2014;53:1058–63. https://doi.org/10.3109/0284186X.2014.927586.
[34] Bahn E, Bauer J, Harrabi S, Herfarth K, Debus J, Alber M. Late contrast enhancing brain lesions in proton-treated patients with low-grade glioma: clinical evidence for increased periventricular sensitivity and variable RBE. Int. J. Radiat. Oncol. Biol. Phys. 2020;107(3):571–8. https://doi.org/10.1016/j.ijrobp.2020.03.013.
[35] Biston M-C, Chiavassa S, Grégoire V, Thariat J, Lacornerie T. Time of PTV is ending, robust optimization comes next. Cancer Radiothe. 2020;24:676–86. https://doi.org/10.1016/j.canrad.2020.06.016.
[36] Timlin C, Loken J, Kruse J, Miller R, Schneider U. Comparing second cancer risk for multiple radiotherapy modalities in survivors of hodgkin lymphoma. Br. J. Radiol. 2021;94:20200354. https://doi.org/10.1259/bjr.20200354.
[37] Brenner DJ, Curtis RE, Hall EJ, Ron E. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. Cancer 2000;88:398–406. https://doi.org/10.1002/(SICI)1097-0142(20000115)88:2<398::AID-CNCR22>3.0.CO;2-V.
[38] Grantzau T, Mellemkjær L, Overgaard J. Second primary cancers after adjuvant radiotherapy in early breast cancer patients: A national population based study under the Danish Breast Cancer Cooperative Group (DBCG). Radiother. Oncol. 2013;106:42–9. https://doi.org/10.1016/j.radonc.2013.01.002.
[39] Wiltink LM, Nout RA, Fiocco M, Meershoek-Klein Kranenbarg E, Jürgenliemk-Schulz IM, Jobsen JJ, et al. No increased risk of second cancer after radiotherapy in patients treated for rectal or endometrial cancer in the randomized TME, PORTEC-1, and PORTEC-2 trials. J. Clin. Oncol. 2015;33:1640–6. https://doi.org/10.1200/JCO.2014.58.6693.
[40] Hall EJ. The impact of protons on the incidence of second malignancies in radiotherapy. Technol. Cancer Res. Treat. 2007;6:31–4. https://doi.org/10.1177/153303460706060S405.
[41] U. Schneider, R. Hälg, The impact of neutrons in clinical proton therapy. Front. Oncol. (2015) doi: 10.3389/fonc.2015.00235.
[42] Vernimmen FJ, Fredericks S, Wallace ND, Fitzgerald AP. Long-term follow-up of patients treated at a single institution using a passively scattered proton beam; observations around the occurrence of second malignancies. Int. J. Radiat. Oncol. Biol. Phys. 2019;103:680–5. https://doi.org/10.1016/j.ijrobp.2018.10.022.
[43] Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. Int. J. Radiat. Oncol. Biol. Phys. 2013;87:46–52. https://doi.org/10.1016/j.ijrobp.2013.04.030.
[44] Buckner J, Giannini C, Eckel-Passow J, Lachance D, Parney I, Laack N, et al. Management of diffuse low-grade gliomas in adults - Use of molecular diagnostics. Nat. Rev. Neurol. 2017;13:340–51. https://doi.org/10.1038/nrneurol.2017.54.