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# Intensity-modulated proton therapy for hippocampal-sparing prophylactic cranial irradiation: a planning comparison with photon therapy

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## Abstract

**Background** The purpose of the study was to evaluate the dosimetric characteristics of volumetric modulated arc therapy (VMAT), helical tomotherapy (HT), and intensity-modulated proton therapy (IMPT) and to compare the dosimetric differences between the two IMPT plans with coplanar and non-coplanar beams in prophylactic cranial irradiation (PCI) with hippocampal-sparing for small cell lung cancer (SCLC).

**Methods** Twenty-five patients diagnosed with limited-stage SCLC and received PCI were enrolled in the study. Four treatment plans were designed: VMAT, HT, and two IMPT plans with coplanar and non-coplanar beams (referred to as IMPT-cop and IMPT-noncop, respectively). The prescription dose was 25 Gy in 2.5 Gy(RBE) fractions. The PTV was optimized in both the VMAT and HT plans. In IMPT plans, multifield optimization and CTV robust optimization with a 3-mm setup uncertainty and 3.5% range uncertainty were used. According to the RTOG 0933 protocol, the dose limits for the hippocampus were the dose received by 100% volume ($D_{100}$) ≤ 9 Gy and the maximum dose ($D_{max}$) ≤ 16 Gy.

**Results** For the target, the two IMPT plans significantly improved the $V_{100}$, $D_{98}$, the homogeneity index (HI) and gradient index (GI) compared with VMAT and HT plans. The HT plans showed the highest conformity index (CI) compared to the other three plans. The two IMPT plans significantly reduced the $D_{100}$, $D_{max}$ and $D_{mean}$ of the hippocampus, the mean dose of bilateral eyeballs and parotids, the maximum dose of bilateral lenses and lenses PRV compared to the VMAT and HT plans. For $D_{100}$ in hippocampus, the IMPT-cop and IMPT-noncop plans reduced by 43.23%, 42.55%, 41.14%, and 40.43%, respectively, relative to VMAT and HT plans. For $D_{max}$ in hippocampus, the IMPT-cop and IMPT-noncop plans decreased by 8.22%, 8.29%, 7.86%, and 7.93%, respectively, relative to VMAT and HT plans. For hippocampal $D_{mean}$, IMPT-cop and IMPT-noncop plans decreased by 23.1%, 22.48%, 20.55%, and 19.91% compared with VMAT and HT plans, respectively. VMAT plans showed the lowest values for the maximum dose to the bilateral eyeballs among the four plans. When comparing the two IMPT plans, IMPT-cop plans significantly reduced the mean dose to the hippocampus, and increased the $D_{mean}$ and $D_{max}$ of bilateral eyeballs, and the $D_{max}$ of bilateral lenses and lenses PRV compared to IMPT-noncop plans.

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**Conclusions** Compared with photon plans, proton plans significantly reduce the dose to the hippocampus, lenses, eyeballs and parotids in hippocampal-sparing PCI. Compared to IMPT plans with coplanar beams, IMPT plans with non-coplanar beams have shown dosimetric advantages in eyeballs and lenses, with no benefit for dose sparing in the hippocampus.

**Keywords** Small cell lung cancer, Prophylactic cranial irradiation, Hippocampal-sparing, Volumetric modulated arc therapy, Helical tomotherapy, Intensity modulated proton therapy

## Introduction

Small cell lung cancer (SCLC) represents approximately 15% of all lung cancers [1]. Brain metastases are common in this tumor type. The incidence of brain metastase (BM) in patients with SCLC is as high as 50%, depending on the stage of the disease [2]. The use of prophylactic cranial irradiation (PCI) results in a significant reduction in BM and an improvement in overall survival for patients with SCLC [3, 4].

Previous studies have confirmed that whole brain radiotherapy is associated with neurocognitive toxicity and have shown a direct relationship between neurocognitive dysfunction and deteriorating quality of life [5, 6]. Hippocampal irradiation is significantly correlated with neurocognitive decline [7, 8].

It is known that pediatric patients may be more sensitive to radiation-induced cognitive deficits than adults, and advanced neurocognitive deficits after radiation therapy in pediatric brain tumors have been identified [9]. Several retrospective studies have shown that the hippocampal dose is associated with cognitive function in children [10, 11]. The results of a 10-year neurocognitive longitudinal study for children and adolescents with low-grade gliomas after radiotherapy showed that a higher hippocampal dose was associated with greater delayed recall decline [12].

With the development of radiation therapy techniques, it has become possible to protect the hippocampus in treatment plans. Previous studies [13, 14] have confirmed that volumetric modulated arc therapy (VMAT) shows a better dosimetry than intensity modulated radiation therapy (IMRT) in hippocampal-sparing whole brain radiotherapy (HS-WBRT). It was proven that helical tomotherapy (HT) demonstrated a further dosimetric advantage over IMRT and VMAT in HS-WBRT [15, 16]. Intensity-modulated proton therapy (IMPT) could improve dose distribution and reduce the dose to organs at risk (OARs) without the limitations of complex anatomy [17, 18]. The application of protons presents an excellent advantage for the protection of OARs in pediatric tumors. Boehling et al. [19] reported that for pediatric patients with craniopharyngiomas, proton therapy can significantly reduce the dose to surrounding normal structures, including the hippocampus, dentate gyrus and subventricular zone. Compared with photon therapy, proton therapy significantly reduces the hippocampal dose and corresponding risk of cognitive impairment in pediatric medulloblastoma patients receiving tumor bed boost irradiation [20].

The accurate delineation of hippocampus is also an important aspect. Bartel [21] et al. found that the delineation of the hippocampus varies greatly among observers, the largest delineation inaccuracy were found in the posterior and anterior-medial border. Previous studies have reported automatic delineation of the hippocampus and these studies all showed satisfactory results [22, 23]. The automatic delineation of hippocampus plays an active role in improving the delineation accuracy and reducing the workload.

A previous study conducted a comparison between HT and IMPT plans for WBRT and discovered that IMPT significantly reduced the $D_{100}$ and $D_{mean}$ to the hippocampus when compared to HT [24]. However, to our knowledge, comprehensive dosimetric comparisons among VMAT, HT, and IMPT for hippocampal-sparing PCI (HS-PCI) in SCLC patients are scarce.

In this study, four plans including VMAT, HT and two IMPT plans with different beams were designed for SCLC cases with HS-PCI. The purpose of the study was to understand the dosimetric characteristics of the three techniques and compare the dosimetric differences between the two IMPT plans with different beams in HS-PCI.

## Materials and methods

### Patient selection and volume delineation

From August 2020 to May 2022, 25 patients diagnosed with limited-stage SCLC and receiving PCI were randomly selected. All patients were simulated in the supine position using thermoplastic masks. All patients underwent computed tomography (CT) and magnetic resonance (MR) simulation scans. In the Varian Eclipse 15.5 treatment planning system (Varian Medical Systems, Palo Alto, CA, USA), CT and MR images were fused and the target and OARs were delineated.

According to the RTOG 0933 atlas definition [25], the hippocampus was delineated using T1-weighted MR imaging axial sequence. The planning risk volume (PRV) of the hippocampus was generated using 5 mm expansion from the hippocampus. The whole brain volume was defined as the clinical target volume (CTV). The planned target volume (PTV) was generated using 3 mm

extension from the CTV and excluding the hippocampal PRV. In the IMPT plans, the CTV for optimization was defined as the whole brain volume minus the PRV of the hippocampus. The brainstem, bilateral optic nerves, eyeballs, lenses, volume of lenses expanded by 3 mm (named as lenses PRV) and spinal cord were delineated. In our study, all four treatment plans were designed using the same structures from a single CT image dataset. all contours of target and OARs were reviewed before the commencement of treatment plan design to ensure the accuracy of the structure delineation, especially the hippocampal contour.

#### Treatment planning

On the CT images of each patient, four treatment plans were designed: VMAT, HT, and two IMPT plans with different beams. The prescription dose was 25 Gy in 2.5-Gy(RBE).

In the Varian Eclipse 15.5 treatment planning system (TPS), VMAT plans were designed on the TrueBeam accelerator. Two 358° full coplanar arcs were adopted and the collimator angles were 70° and 300°, respectively. Six megavolt X-ray was used. The dose calculation algorithm was analytic anisotropic algorithm (AAA).

HT plans were designed in the Tomotherapy version 5.1.3 TPS (Accuray R Planning Station, Madison, WI, USA). A field width of 1.05 cm and a pitch of 0.43 were used in the plan. The modulation factor was initially set to 1.8 and was adjusted throughout the optimization. The PTV was optimized in both the VMAT and HT plans.

The IMPT plans were generated in Varian Eclipse for the ProBeam proton system. In the first IMPT plan (IMPT-cop), right and left lateral beams and a posterior beam were used. The second IMPT plan (IMPT-noncop) employed right and left lateral beams and a non-coplanar beam (superior anterior oblique beam) at gantry angle of 50° with a 270° couch rotation according to the IEC61217 coordinate system. The gantry angle of 50° and couch rotation of 270° were chosen to allow the beam to enter obliquely from the anterior aspect of the skull, which facilitates the avoidance of the eyes and lenses. In IMPT plans, multifield optimization (MFO) and robust optimization with a 3-mm setup uncertainty and 3.5% range uncertainty were used. The CTV was optimized in the IMPT plans. For all the proton beams, a range shifter with a thickness of 5 cm was used.

According to the RTOG 0933 protocol, the dose limits for the hippocampus were the dose received by 100% volume ($D_{100}$) ≤ 9 Gy and the maximum dose ($D_{max}$) ≤ 16 Gy [25]. The optimization goals of all the plans were to ensure the dose coverage of target while minimizing the dose to the OARs.

#### Dosimetric evaluation

For the target, the irradiated doses of 2% and 98% volume ($D_2$, $D_{98}$) and the volume surrounded by the prescription dose ($V_{100}$) were analyzed. In photon plans, the index of the target analyzed is the index of PTV, while in proton plans, the target represents CTV. The conformity index (CI), the homogeneity index (HI) and gradient index (GI) of the target were evaluated with the following Eqs. (1), (2),and (3), respectively.

$$\mathrm{CI} = \frac{TV_{PV}{}^2}{TV \times PV} \tag{1}$$

The $TV_{PV}$ represents the volume of the target surrounded by the prescription dose, TV represents the volume of the target and PV represents the total volume surrounded by the prescription dose.

$$\mathrm{HI} = \frac{D_2 - D_{98}}{D_p} \tag{2}$$

The $D_2$ and $D_{98}$ represent the irradiated doses of 2% and 98% volumes of target, respectively. $D_p$ represents the prescription dose.

$$\mathrm{GI} = \frac{V_{50}}{V_{100}} \tag{3}$$

The $V_{50}$ and $V_{100}$ represent the volumes surrounded by the 50% and 100% prescription dose lines, respectively.

For the target related metrics calculated in the above formulas, the relevant metrics of PTV were analyzed in photon plans, while the relevant indicators of CTV were analyzed in proton plans.

For the hippocampus, $D_{100}$, $D_{max}$, and the mean dose ($D_{mean}$) were analyzed. The maximum doses ($D_{max}$) to the lenses, lenses PRV, optic nerves, brainstem and spinal cord were analyzed. For eyeballs, the mean dose ($D_{mean}$) and the maximum dose ($D_{max}$) were analyzed.

#### Statistical analysis

The Statistical Package for Social Sciences v19.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Friedman's two-way analysis of variance by ranks test for multiple samples was used to compare the four plans. The Wilcoxon matched-paired signed-rank test was used to evaluate the significance of the observed differences between the IMPT-cop and IMPT-noncop plans. Differences were considered to be statistically significant when $p < 0.05$.

## Results

### Patients and volumes

Table 1 shows the patient characteristics. The average volume of the left hippocampus was 2.79 ± 1.59 $cm^3$. The average volume of the right hippocampus was 2.72 ± 1.49 $cm^3$.

### Dose comparisons for IMPT plans and the other two photon plans

Table 2 shows the dosimeric parameters of the target (CTV/PTV) and OARs for the four plans. The two IMPT plans significantly increased the $V_{100}$ and $D_{98}$ of the target compared with the VMAT and HT plans. For $D_2$ of the target, the two IMPT plans significantly reduced the values compared to VMAT plans and no significant differences were detected between the IMPT plans and HT plans. Compared with the two IMPT plans, the HT plans increased the CI. No significant differences were found between the two IMPT plans and VMAT plans in CI. The two IMPT plans significantly reduced the values of HI and GI compared with those of the VMAT and HT plans.

For the hippocampus, the $D_{100}$, $D_{max}$ and $D_{mean}$ were significantly lower in the two IMPT plans than in the VMAT and HT plans ($p < 0.001$). For the bilateral eyeballs, the two IMPT plans significantly reduced the mean dose compared to the VMAT and HT plans. The IMPT-cop plans increased the maximum dose to the bilateral eyeballs compared to the VMAT plans, and the IMPT-noncop plans reduced this metric compared to the HT plans. For the maximum dose to the bilateral lenses, bilateral lenses PRV, and the mean dose to the bilateral parotids, the two IMPT plans significantly reduced the values compared to the two photon plans. For the maximum dose to the bilateral optic nerves, the IMPT-cop plans showed lower values compared to VMAT plans, and no significant differences were detected between the two IMPT plans and the HT plans. The two IMPT plans reduced the maximum dose to the brainstem compared to the VMAT plans, and meanwhile, this metric was increased in the two IMPT plans than in the HT plans. The IMPT-noncop plans increased the maximum dose of spinal cord compared to HT plans. No significant differences were detected between the IMPT-cop plans and the VMAT or HT plans. Figure 1 shows the dose distributions of the four plans for a representative patient. Figure 2 and Supplementary Figs. 1–3 show the dose-volume histograms of the PTV and OARs for the four plans.

**Table 1** Patient characteristics (number = 25)

| Characteristic | |
|---|---|
| Median age (years) | 63(41–79) |
| | Number of patients |
| Gender | |
| Male | 20 |
| Female | 5 |
| Stage of disease | |
| Limited | 25 |
| Extensive | 0 |
| Clinical AJCC stage | |
| IIA | 7 |
| IIB | 9 |
| IIIA | 9 |

AJCC, American Joint Committee on Cancer

### Dose comparisons for the two IMPT plans

For the CTV, no significant differences were observed in $V_{100}$, $D_{98}$, or CI between the two IMPT plans. IMPT-cop plans presented lower $D_2$ and HI and greater GI compared to IMPT-noncop plans.

For the OARs, IMPT-cop plans significantly reduced the mean dose to the hippocampus compared to IMPT-noncop plans ($p = 0.006$). No significant differences were observed in $D_{100}$ or $D_{max}$ of hippocampus between the two plans. For the $D_{mean}$ and $D_{max}$ of bilateral eyeballs, and the $D_{max}$ of bilateral lenses and lenses PRV, significant decreases were achieved with the IMPT-noncop plans compared to the IMPT-cop plans. No significant differences were observed in the maximum dose to the bilateral optic nerves, brainstem, or spinal cord or in the mean dose to the bilateral parotids between the two IMPT plans.

### Dose comparisons for the VMAT and the HT plans

For the PTV, lower $D_2$ and HI and greater CI and GI were observed in the HT plans than in the VMAT plans, and no significant differences were found in $D_{98}$ or $V_{100}$ between the two plans.

Compared with those of the VMAT plans, the $D_{100}$ and $D_{mean}$ of the hippocampus were lower in the HT plans, but no significant differences were found in the maximum dose to the hippocampus between the two plans. The maximum and mean doses to the bilateral eyeballs in the HT plans were significantly higher than those in the VMAT plans. Moreover, compared with the VMAT plans, the HT plans significantly reduced the maximum dose to the bilateral lenses, lenses PRV, optic nerves, brainstem, and spinal cord and the mean dose to the bilateral parotids.

## Discussion

For SCLC patients, the use of the PCI has been shown to reduce the incidence of BM and prolong disease-free survival [3, 4], but the PCI could affect the development of neurocognitive dysfunction. In recent years, the hippocampus, a region that may be more sensitive to radiation therapy than other regions of brain, has been found to be particularly prominent in terms of cognitive decline [26]. Preclinical and human studies have suggested that

**Table 2** Dosimetric analysis of the four hippocampal-sparing plans

| | IMPT-cop | IMPT-noncop | VMAT | HT | $p < 0.05$ |
|---|---|---|---|---|---|
| **CTV/PTV** | | | | | |
| $V_{100}$ (%) | 98.30 ± 0.16 | 98.25 ± 0.18 | 95.85 ± 0.70 | 95.72 ± 0.53 | a, b,c, d |
| $D_2$ (Gy) | 26.81 ± 0.14 | 26.85 ± 0.17 | 27.26 ± 0.16 | 26.57 ± 0.28 | a, c,e, f |
| $D_{98}$ (Gy) | 25.10 ± 0.07 | 25.10 ± 0.08 | 23.84 ± 0.44 | 23.82 ± 0.36 | a, b,c, d |
| CI | 0.87 ± 0.01 | 0.87 ± 0.01 | 0.86 ± 0.02 | 0.91 ± 0.03 | b, d,f |
| HI | 0.07 ± 0.01 | 0.07 ± 0.01 | 0.14 ± 0.02 | 0.11 ± 0.02 | a, b,c, d,e, f |
| GI | 1.53 ± 0.03 | 1.51 ± 0.04 | 1.58 ± 0.07 | 1.74 ± 0.10 | a, b,c, d,e, f |
| **Hippocampus** | | | | | |
| $D_{100}$ (Gy) | 4.95 ± 0.65 | 5.01 ± 0.65 | 8.72 ± 0.39 | 8.41 ± 0.60 | a, b,c, d,f |
| $D_{max}$ (Gy) | 13.95 ± 0.62 | 13.94 ± 0.73 | 15.20 ± 0.58 | 15.14 ± 0.40 | a, b,c, d |
| $D_{mean}$ (Gy) | 8.62 ± 0.14 | 8.69 ± 0.17 | 11.21 ± 0.52 | 10.85 ± 0.71 | a, b,c, d,e, f |
| **Eyeball-L** | | | | | |
| $D_{mean}$ (Gy) | 2.91 ± 1.06 | 2.11 ± 0.77 | 7.73 ± 0.96 | 9.22 ± 0.76 | a, b,c, d,e, f |
| $D_{max}$ (Gy) | 20.57 ± 2.43 | 19.62 ± 2.74 | 19.18 ± 2.47 | 21.37 ± 2.11 | a, d,e, f |
| **Eyeball-R** | | | | | |
| $D_{mean}$ (Gy) | 3.00 ± 1.00 | 2.25 ± 0.74 | 7.91 ± 0.91 | 9.27 ± 0.72 | a, b,c, d,e, f |
| $D_{max}$ (Gy) | 20.09 ± 1.90 | 19.37 ± 1.97 | 18.81 ± 2.77 | 21.02 ± 2.22 | a, d,e, f |
| **Lens-L** | | | | | |
| $D_{max}$ (Gy) | 0.68 ± 0.67 | 0.28 ± 0.38 | 5.16 ± 0.83 | 3.71 ± 0.35 | a, b,c, d,e, f |
| **Lens-L PRV** | | | | | |
| $D_{max}$ (Gy) | 1.60 ± 1.37 | 0.74 ± 0.81 | 6.13 ± 0.92 | 4.93 ± 0.42 | a, b,c, d,e, f |
| **Lens-R** | | | | | |
| $D_{max}$ (Gy) | 0.78 ± 0.54 | 0.34 ± 0.36 | 5.22 ± 0.79 | 3.61 ± 0.36 | a, b,c, d,e, f |
| **Lens-R PRV** | | | | | |
| $D_{max}$ (Gy) | 1.94 ± 1.32 | 0.98 ± 0.89 | 6.25 ± 0.91 | 4.85 ± 0.37 | a, b,c, d,e, f |
| **Opt-L** | | | | | |
| $D_{max}$ (Gy) | 25.11 ± 0.62 | 25.34 ± 0.51 | 25.78 ± 0.90 | 25.07 ± 0.80 | a,f |
| **Opt-R** | | | | | |
| $D_{max}$ (Gy) | 25.21 ± 0.61 | 25.31 ± 0.46 | 25.66 ± 0.91 | 25.14 ± 0.67 | a, f |
| **Brainstem** | | | | | |
| $D_{max}$ (Gy) | 27.26 ± 0.29 | 27.26 ± 0.33 | 27.67 ± 0.23 | 26.77 ± 0.23 | a, b,c, d,f |
| **Spinal cord** | | | | | |
| $D_{max}$ (Gy) | 25.99 ± 2.49 | 26.28 ± 1.57 | 26.46 ± 1.63 | 25.64 ± 1.43 | d, f |
| **Parotid-L** | | | | | |
| $D_{mean}$ (Gy) | 0.83 ± 0.50 | 0.85 ± 0.50 | 4.39 ± 1.07 | 3.26 ± 0.78 | a, b,c, d,f |
| **Parotid-R** | | | | | |
| $D_{mean}$ (Gy) | 1.09 ± 0.68 | 1.12 ± 0.63 | 4.69 ± 0.73 | 3.32 ± 0.67 | a, b,c, d,f |

a: IMPT-cop vs. VMAT, b: IMPT-cop vs. HT, c: IMPT-noncop vs. VMAT, d: IMPT-noncop vs. HT, e: IMPT-cop vs. IMPT-noncop, f: VMAT vs. HT, Eyeball-L: left eyeball, Eyeball-R: right eyeball, Lens-L: left lens, Lens-R: right lens, Opt-L: left optic nerve, Opt-R: right optic nerve

bilateral or unilateral hippocampal radiation damage may be a key cause of neurocognitive decline [27, 28].

Due to the physical characteristics of protons, previous studies have confirmed that protons can better spare the doses of OARs than photons [29, 30]. With the development of modern proton technique, IMPT can obtain a significantly superior dose distribution for targets with complex shapes, can form conformal doses around the target, and can thus optimally protect the normal tissues [17, 18, 31].

In this study, for the target, both IMPT plans increased the dose coverage, as shown by improvements in $V_{100}$ and $D_{98}$ compared to the VMAT and HT plans. The ability of IMPT to improve target coverage has been recognized [17, 24]. Mizuno et al. [32] compared VMAT, HT and IMPT for angiosarcoma of the scalp, and reported that the lowest $D_2$ of the target was shown in HT plans. The same results were shown in our study, but no statistical differences were found between the IMPT and HT plans in terms of this parameter. Both IMPT plans showed the best HI and GI compared to VMAT and HT plans. For the target conformity, the IMPT plans improved this index compared with VMAT plans, but worse than HT plans. The IMPT plans were designed based on the robust optimization of CTV coverage. The CI was calculated for CTV in the IMPT plans, which was different

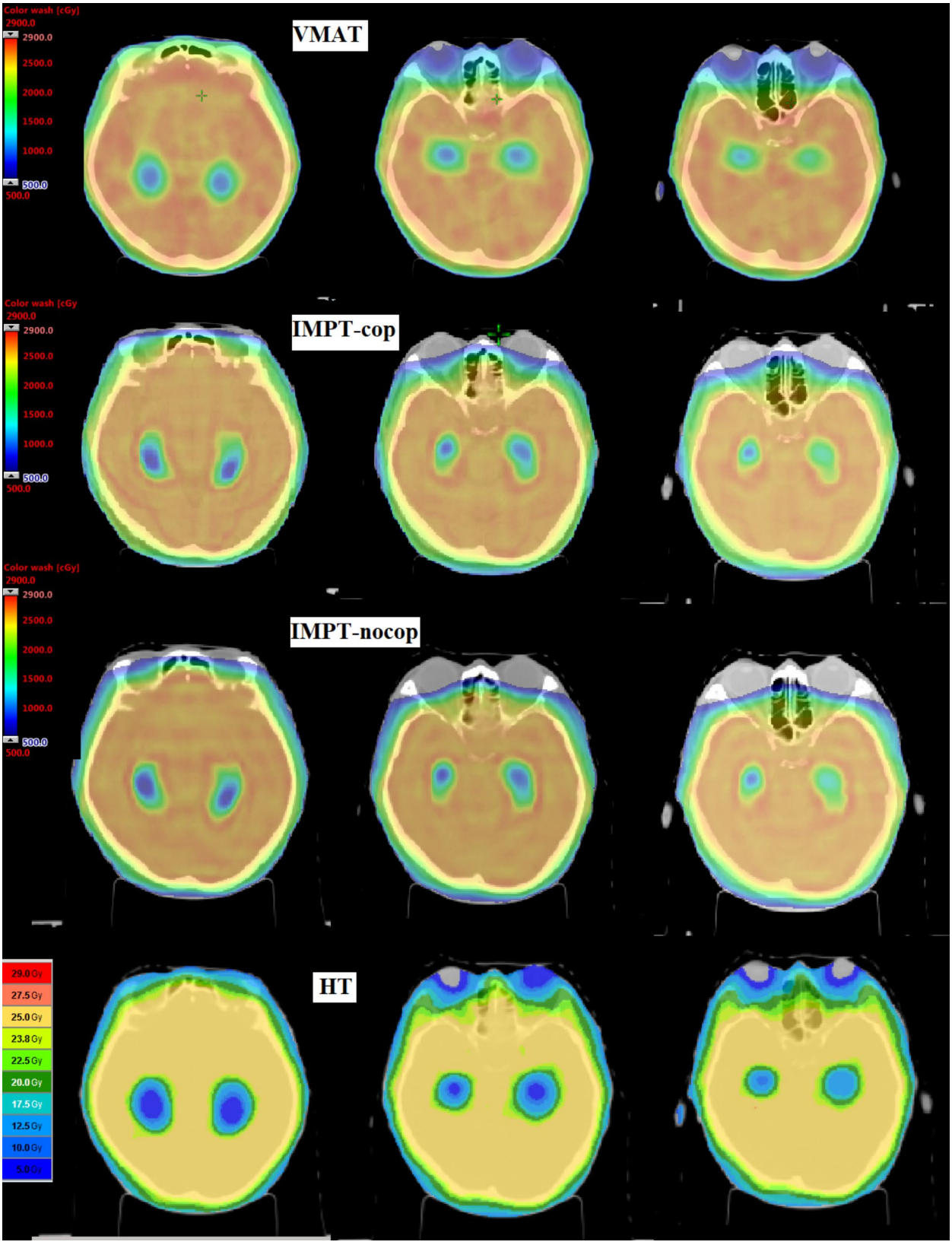


**Fig. 1** The dose distributions of the four plans for a representative patient. The images show VMAT, IMPT-cop, IMPT-noncop, and HT plans from the top row to the bottom row

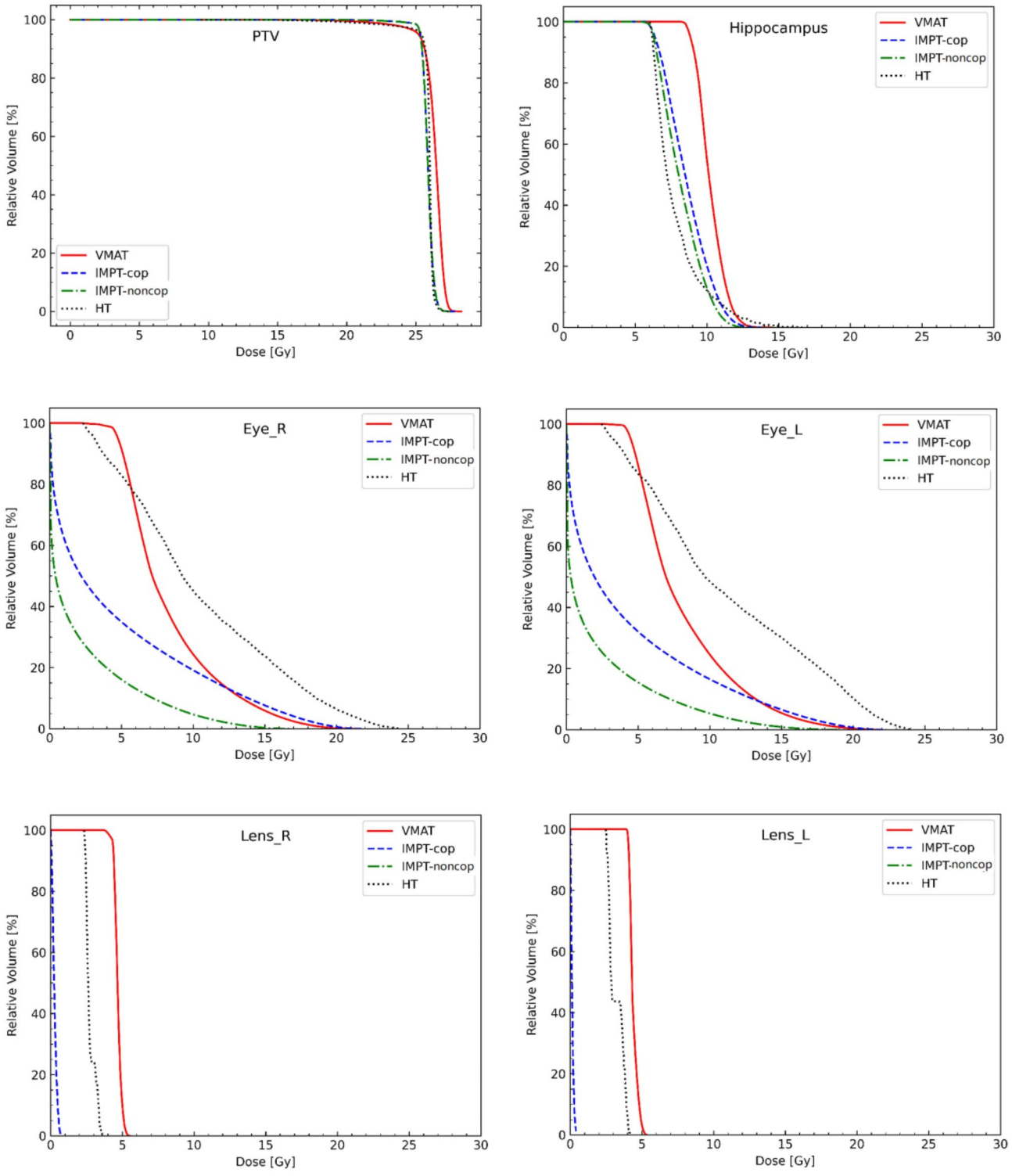


**Fig. 2** Dose–volume histograms of the PTV and OARs of the four plans for a representative patient (Note: In the IMPT-noncop plan, the maximum doses to the right and left lenses were extremely low, at 0.018 Gy and 0.051 Gy, respectively. Due to these minimal doses, the corresponding DVH curve for the lenses in the IMPT-noncop plan is not visually discernible on the figure. The doses are so low that they only manifest as a single data point, which cannot be effectively plotted alongside the other plans)

from that in the photon plans. Due to the robust optimization, the prescription dose did not closely adhere to the boundary of the CTV but rather at a certain distance, resulting in a relatively large volume of prescription dose coverage. This may be the reason why the CI in the IMPT plans was lower than that in the HT plans.

The RTOG 0933 protocol revealed that a dose of more than 9 Gy in the $D_{100}$ of hippocampus and a maximum hippocampal dose of more than 16 Gy were associated with memory functional impairment in WBRT of 30 Gy in 10 fractions. In their study, dose to 100% of the hippocampus exceeding 10 Gy and maximum dose of hippocampus exceeding 17 Gy were considered unacceptable [25]. In the present study, all four plans met this dose requirement. The $D_{100}$, $D_{max}$ and $D_{mean}$ of the hippocampus were significantly lower in the IMPT plans than in the VMAT and HT plans. Early neurocognitive decline, such as short-term memory loss and language impairment, may occur within 4 months after WBRT in patients with brain metastases [5, 33, 34]. Because the doses to hippocampus are considered to be the main factor involved in neurocognitive decline [7, 8], IMPT is more beneficial for hippocampal preservation than photon therapy. Takaoka et al. [24] compared HT and IMPT plans for WBRT and found that IMPT significantly reduced the $D_{100}$ and the $D_{mean}$ of the hippocampus compared with HT. Their results are the same as ours. In their study, the $D_{max}$ of the hippocampus was slightly higher in the IMPT plans than in the HT plans. These findings are different from our findings. In our study, the maximum dose to the hippocampus was significantly lower in the IMPT plans than in the HT plans, which may be related to our strict dose limitation on the hippocampus during the design of the IMPT plans. This may also explain why the $D_2$ of the target in the IMPT plans were slightly greater than those in the HT plans in our study, as the $D_2$ in IMPT plans were lower than those in HT plans in their study.

When comparing the two proton plans, we found that the mean doses to the hippocampus were lower in the IMPT-cop plans than in the IMPT-noncop plans ($8.62 \pm 0.14$ Gy vs. $8.69 \pm 0.17$ Gy, $p = 0.006$). Although the differences were statistically significant, we found that the numerical differences in the above index between the two IMPT plans were small, at approximately 0.07 Gy. These differences may not be clinically significant. Popp et al. [35] compared HA-WBRT VMAT plans with SIB and found that using a complete directional hippocampal blocking reduced the mean hippocampal dose from $10.07 \pm 0.96$ Gy to $8.79 \pm 0.99$ Gy. In our study, we did not use a blocking technique. The cases in this study were patients with SCLC, which has a high incidence of brain metastasis. To avoid under-dosing of the brain tissue surrounding the hippocampus, we did not impose very strict dose constraints on the hippocampus. In this study, the mean doses to the hippocampus in the proton plans were slightly lower than the results in Popp's study, but not as significant as the reduction in $D_{100}$. The main reason may be the strict dose requirements for the target and the impact of robustness optimization. For photon plans, HT was considered to be a beneficial technique in the WBRT with hippocampal sparing, and previous studies have confirmed this [15, 16]. The same dosimetric results were demonstrated in our study, in which the HT plans reduced the dose to the hippocampus relative to the VMAT plans. Sun et al. [36] compared the dosimetric differences between the traditional C-arm accelerators and the new O-ring accelerator (Halcyon) in HS-PCI for SCLC cases, and found that the dose to the hippocampus in Halcyon could be significantly lower than that in C-arm accelerators. The Halcyon plans were not addressed in our study, and future studies could attempt to compare dosimetric differences between Halcyon and HT.

According to the international guidelines for radiotherapy planning for nasopharyngeal carcinoma, the dose limits for the eyeball are recommended to be less than 35 Gy for the mean dose and $D_{0.03cc} \leq 50$ Gy, and the dose limit for the lens is $D_{0.03cc} \leq 15$ Gy [37]. In our study, all four plans met the recommended dose limits. Compared to the VMAT and HT plans, the two IMPT plans significantly reduced the mean dose to bilateral eyeballs and the maximum dose to the bilateral lenses and bilateral lenses PRV. The maximum doses of lenses in the IMPT plans were less than 1 Gy. Our results are identical to those of previous studies [32, 38]. During plan optimization, the maximum doses of the eyeballs were not constrained. For the maximum dose of eyeballs, the VMAT plans had the lowest values among all plans. The main reason may be that when optimizing the VMAT plans, we limited the mean dose to the eyeball to further reduce the maximum dose to the lens. This is one of our experiences when designing radiotherapy plans for head and neck tumors to reduce the doses to lenses. In the HT plans, the doses to the lenses were mainly reduced by setting the region of lens expansion 3 mm to complete block. The IMPT plans reduces the doses of lenses mainly through its physical characteristics. Neither of these two plans required lowering the doses of lenses by lowering the doses of eyeballs. In the VMAT plans, lowering the mean doses to the eyeballs also indirectly reduces the maximum doses to the eyeballs. This may be the reason why the VMAT plans has lower maximum doses of eyeballs than HT and IMPT plans. Jiang et al. [16] reported that the HT plans reduce the maximum dose to the lens and increase the maximum dose to the eyeball relative to the VMAT plans for HS-WBRT. This finding is also consistent with our findings.

A previous study revealed that the maximum dose applied to the optic nerve was greater in IMPT plans than in HT plans for HS-WBRT [24]. Similar results were also found in our study. The maximum doses to the optic nerves in the IMPT plans were slightly higher than those in the HT plans, but the difference was not statistically significant. The proximity of the optic nerves to the target and the robust optimization may also explain why the doses of optic nerves in the proton plans could not be further reduced.

For the maximum doses to the brainstem and spinal cord, the HT plans showed the lowest values compared to VMAT and IMPT plans. The previous two parameters were lower in both IMPT plans than in the VMAT plans. The previously mentioned international guidelines for nasopharyngeal carcinoma suggest that the recommended doses for the brainstem and spinal cord are $D_{0.03cc}$ of PRV less than 54 and 45 Gy, respectively [37]. In this study, the maximum doses for the brainstem and spinal cord were much lower than the above recommended doses. The dose limitations on the brainstem and spinal cord were not hard constraints when we performed the plan optimization, and the optimization mainly focused on the hippocampal dose limitation, which may also be responsible for this result.

For the two IMPT plans, the target had similar dosimetric results. Although there were statistical differences in $D_2$, HI, and GI between the two plans, the differences in the mean values of the three parameters were very small and may not be clinically significant. IMPT plans with coplanar fields significantly reduced the mean dose to the hippocampus compared to IMPT plans with non-coplanar fields. The doses of eyeballs and lenses were found to be lower in IMPT plans with non-coplanar fields. This is because in the IMPT-noncop plans, the non-coplanar field enters obliquely from the front of the cranium, avoiding eyeballs outside the range of the field. A previous study reported that non-coplanar VMAT can reduce the hippocampal dose for postoperative primary brain tumors [39]. It has also been reported that non-coplanar VMAT can improve the uniformity of the target and decrease the dose of the hippocampus in HS-WBRT [40]. In our study, the coplanar VMAT plans we designed achieved hippocampal doses similar to those in the previous study. The rotation of the couch during treatment may introduce dose uncertainty and increase the treatment time. Dosimetric comparison of the two IMPT plans revealed that the non-coplanar field did not result in a reduction in the hippocampal dose. In practice, the field direction in IMPT plans can be selected according to the specific characteristics of the patient. For example, if the eyeball or lens dose needs to be further reduced, a non-coplanar field can be selected.

In summary, compared with photons, proton therapy can achieve very sharp dose gradients through physical differences in energy deposition, thus showing dosimetric advantages for hippocampal sparing. The emerging technique, spot-scanning proton arc therapy, also demonstrated superior dosimetric advantages in whole-brain radiotherapy with hippocampal sparing, and simultaneously significantly reduced delivery time compared with conventional proton technique [41].

Compared with photon therapy, proton therapy has demonstrated a high disease control rate and acceptable toxicity in skull-based malignancies [42]. For radiotherapy of brain tumors, proton therapy has the potential to reduce adverse effects, especially cognitive impairment [18]. For Grade II gliomas, Shih et al. [43] reported that proton therapy could protect cognitive function and maintain quality of life. Unlike the above studies, our study was based on planning dosimetry rather than clinical outcomes, which was a limitation of this study. Dose-response models can be used to assess differences in clinical impact due to dosimetric differences among different treatment plans. To the best of our knowledge, a reliable model for the brain has yet to be developed. Consistent with the findings of previous study [38], we also believe that it is appropriate to maintain the hippocampus as low as possible. However, further prospective studies are needed to verify whether the dosimetric advantage of protons can improve cognitive function. Although no clinical data were included, we believe that the proton technique may be clinically meaningful due to the significant reduction in doses to the hippocampus, lenses, and eyeballs.

## Conclusions

In hippocampal-sparing PCI for SCLC patients, compared with photon plans, proton plans improve the target coverage and dose uniformity, and significantly reduce the dose to the hippocampus and other OARs. Compared with coplanar proton plans, non-coplanar proton plans could significantly reduce the doses of the lenses and the eyeballs, but had no benefit on the improving the hippocampal dose. In practice, a suitable beam mode can be selected according to the individual characteristics of the patient. In photon therapy plans, tomotherapy demonstrate more dosimetric advantages than VMAT, which is recommended for HS-PCI patients in institutions.

with the HT technique.

**Abbreviations**

| | |
|---|---|
| SCLC | Small cell lung cancer |
| BM | Brain metastase |
| PCI | Prophylactic cranial irradiation |
| VMAT | Volumetric modulated arc therapy |
| IMRT | Intensity modulated radiation therapy |
| HS | Hippocampal-sparing |
| WBRT | Whole brain radiotherapy |

| | |
|---|---|
| HT | Helical tomotherapy |
| IMPT | Intensity-modulated proton therapy |
| OAR | Organ at risk |
| CT | Computed tomography |
| MR | Magnetic resonance |
| PRV | Planning risk volume |
| CTV | Clinical target volume |
| PTV | Planned target volume |
| RBE | Relative biological effectiveness |
| TPS | Treatment planning system |
| AAA | Analytic anisotropic algorithm |
| MFO | Multiple-field optimization |
| CI | Conformity index |
| HI | Homogeneity index |
| GI | Gradient index |

## Supplementary Information

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Supplementary Material 1

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Not applicable.

**Author contributions**
YY and TS designed the study; GZ collected the CT data; XY, TS and XL designed the treatment plans; GZ and XL analyzed the data; XY and TS wrote the paper. All authors read and approved the final manuscript.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Ethics approval was obtained from the local ethics committee of Affiliated Cancer Hospital of Shandong First Medical University (ethical approval number: SDTHEC2023008024). The study was in Accordance with the declaration of Helsinki principles. The need for an informed consent was waived by the Ethics Committee of Affiliated Cancer Hospital of Shandong First Medical University due to the retrospective nature of the study.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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