Radiation Oncology

RESEARCH

Open Access

Dummy run study for outlining and plan quality of intensity-modulated radiotherapy in elderly patients with newly diagnosed glioblastoma: The Japan clinical oncology group study JCOG1910 (AgedGlio-PIII)

Tomohiro Ono[1,2*], Megumi Uto[2], Yohei Mineharu[3], Yoshiki Arakawa[3], Mitsuhiro Nakamura[4], Teiji Nishio[5], Hiroshi Igaki[6], Keiji Nihei[7], Satoshi Ishikura[8], Yoshitaka Narita[9], Takashi Mizowaki[2] and Brain Tumor Study Group and Radiation Therapy Study Group of the Japan Clinical Oncology Group

Abstract

Background A dummy run was conducted to ensure the quality of intensity-modulated radiotherapy (IMRT) before registration in a randomized phase III study of elderly patients with newly diagnosed glioblastoma by the Japan Clinical Oncology Group 1910 (JCOG1910).

Methods All 41 institutions enrolled in this study were required to report outlining that included gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), and treatment planning for one benchmark case. First, deviations in outlining were evaluated using the Dice similarity coefficient (DSC) and mean distance agreement (MDA), compared to reference targets delineated by the research secretariat. Second, the participating institutions were required to create treatment plans for arms A (40.05 Gy in 15 fractions) and B (25 Gy in 5 fractions) using IMRT techniques. The quality of the outlining and dose-volume criteria for each target and organs at risk were evaluated.

Results Six institutions failed to adhere to the protocol and required revision due to insufficient GTV outlining, not considering anatomical barriers for CTV, and modifying PTV against protocols. Compared to the reference outlining, the means and standard deviations of DSC and MDA were 0.37 ± 0.19 and 9.41 ± 3.99 mm for GTV; 0.80 ± 0.08 and 4.31 ± 1.85 mm for CTV; and 0.83 ± 0.05 and 4.23 ± 1.45 mm for PTV, respectively. Regarding dose-volume criteria, 40 of the 41 institutions met the per-protocol limits; only one was within the acceptable limits.

Conclusions Several institutions demonstrated deviations in outlining that necessitated revisions. Thus, appropriate feedback and periodic sharing of information with participating institutions is necessary in the upcoming prospective JCOG1910 study.

Keywords Dummy run study, Elderly patients with newly diagnosed glioblastoma, JCOG1910, Outlining

*Correspondence:
Tomohiro Ono
tono@kuhp.kyoto-u.ac.jp

Full list of author information is available at the end of the article

Background

Glioblastoma is the most prevalent malignant primary brain tumor, with an increasing incidence-adjusted rate for age [1, 2]. A dose of 60 Gy in 30 fractions with concomitant and adjuvant temozolomide currently represents the standard radiotherapy regimen for patients with glioblastoma aged < 70 years [3–5]. Although several studies have used this prescribed dose for elderly patients with newly diagnosed glioblastoma and showed prolonged overall survival, they also noted certain treatment-related toxicities, including mental deterioration [6, 7]. Moreover, concerns exist regarding the low completion rates for this treatment, owing to its prolonged duration and the decline in activities of daily living often experienced by the patients. Consequently, hypofractionated radiotherapy has been used in several trials to overcome treatment-related toxicities [1, 8–10]. However, these studies were limited by small sample sizes, leaving the optimal dose and fractionation schedule uncertain, especially in combination with temozolomide. Recently, the Brain Tumor Study Group and the Radiation Therapy Study Group (RTSG) of the Japan Clinical Oncology Group (JCOG) have initiated a multi-institutional randomized controlled phase III trial in elderly patients with newly diagnosed glioblastoma (JCOG1910, AgedGlioPIII) [11]. The JCOG1910 study involves chemoradiotherapy combined with temozolomide, wherein a total of 270 patients will be registered initially, followed by 264 in a second registration wave. Prescribed doses of 40.05 Gy delivered in 15 fractions and 25 Gy in five fractions have been set for arms A and B of the study, respectively. JCOG1910 allows for three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and volumetric modulated arc therapy (VMAT). All participating institutions must pass the dosimetric auditing system of the Medical Physics Working Group of the JCOG-RTSG to be eligible to administer IMRT or VMAT within the context of the JCOG1910 [12], as well as participate in a dummy run study designed by JCOG1910. This is because it is necessary to confirm that outlining is performed appropriately and treatment plans are created adequately, to ensure treatment efficacy in a multi-institution clinical trial of radiotherapy.

Quality assurance (QA) for radiation therapy plays an important role in ensuring consistent quality between clinical trials [13]. QA in clinical trials includes a benchmark case, credentialing, and individual cases. Brooks et al. reported that QA of outlining in a benchmark case is crucial for ensuring protocol compliance [14]. Additionally, Weber et al. suggested that QA of a benchmark case would potentially impact patient outcomes [15]. Thus, standardization of outlining and treatment plan quality is essential for clinical trials. Musat et al. performed a dummy run for the EORTC 22,033–26,033 trial, which randomized between radiotherapy and temozolomide as the initial treatment for patients with low-grade glioma. They evaluated the outlining and conformity indexes of 40 academic institutions [16]; only two were requested to repeat outlining, whereas most conformed to the protocol's requirements. Similarly, several studies have compared dummy runs and individual case reviews and reported that combining the two was highly effective [17–19]. Accordingly, participation in a dummy run has been set as a requirement for every institution that uses IMRT or VMAT within the JCOG1910 study.

This study aimed to assess outlining and treatment plans for JCOG1910 during a dummy run study across multiple institutions, with the aim of contributing to the standardization of both outlining and the quality of treatment plans for newly diagnosed glioblastoma.

Methods

Dummy run case information

A benchmark case suitable for the JCOG1910 protocol was selected for this dummy run study. The patient was diagnosed with glioblastoma and treated using surgery, radiotherapy, and concomitant adjuvant temozolomide [11]. The patient underwent both computed tomography (CT) and magnetic resonance (MR) imaging. The CT images had a slice thickness of 2 mm. The MR images were acquired both pre- and postoperatively and included fluid-attenuated inversion recovery (FLAIR) and contrast-enhanced (CE) weighted-T1 images. The MR scans had a slice thickness of < 5 mm. The structures of the organs at risk (OARs)—including the left retina (Retina_L), right retina (Retina_R), brain stem, spinal cord, cerebrum, left optic nerve (Optic Nerve_L), right optic nerve (Optic Nerve_R), chiasm, left lens (Lens_L), and right lens (Lens_R)—were delineated as the reference data set.

Dummy run examination content

Each institution was asked to delineate target volumes—including gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV)—as well as plan the treatment. GTV was delineated based on the CT and MR images, if any residual tumor was present. The dummy run case defined residual tumor as GTV. CTV was delineated considering structural changes following surgery and residual tumors visible on images, as well as structures that serve as anatomic barriers (e.g., the cerebral falx and tent). CTV was determined by adding a margin of 15 mm to the GTV plus the resection cavity, and a high signal intensity area on postoperative MR FLAIR images. However, a reduction in the CTV was permitted when it was adjacent to an OAR or to account for anatomical barriers. PTV was determined by adding

a margin of 3–5 mm, in accordance with the setup policy of each institution.

Each institution planned their A and B arms using IMRT or VMAT and created plans for their delineated targets. Table 1 shows the dose and dose-volume criteria for the target volumes and OARs. The prescribed dose was defined as the dose receiving 50% ($D_{50\%}$) of the PTV based on the recommendation of International Commission on Radiation Units and Measurements (ICRU) Report 83 [20]. This is because the JCOG1910 study also allows reference point prescription with 3DCRT, and for IMRT or VMAT, the D50% prescription is considered to correspond best with the ICRU reference point. A range of 98–102% of the prescribed dose was defined as per the protocol, and a range of 95–105% of the prescribed dose was defined as the acceptable variation for the $D_{50\%}$ of the PTV. Volumes receiving 90% of the prescribed dose ($V_{90\%}$) and $D_{2\%}$ of the PTV, which correspond to the near-minimum and near-maximum dose, respectively, were defined as other dose-volume criteria. The dose-volume criteria for OARs were defined based on Emami et al. [21] and Marks et al. [22]. In addition, the criteria adhered to those established in a previous study of JCOG1703 [5] and are specified for arms A and B based on the total dose, calculated using the LQ model with a 2 Gy per fraction equivalent dose. Dose calculation algorithms—type "b" or "c"—were used to calculate all doses to ensure high accuracy [23–25]. The target dose calculation grid size was ≤ 2.5 mm. Each treatment machine was required to have a multi-leaf collimator with an energy of ≥ 4 MV.

Evaluation of outlining

Outlining was confirmed by the research secretariat to ensure compliance with the study protocol. If a target did not comply, the institution was required to revise it according to the protocol. The Dice similarity coefficient (DSC) and mean distance agreement (MDA) were calculated to evaluate target variations using MIM Maestro version 7.3.2 (MIM Software Inc., Cleveland, OH, USA). The reference target was defined by the research secretariat. A total of 41 outlinings were evaluated. All treatment plans also came from the same 41 institutions.

Evaluation of treatment planning

In total, 82 plans (including both study arms) were evaluated to ensure the dose-volume criteria. The dose-volume criteria for the targets and OARs were confirmed for each study arm. The variation in each dose-volume criterion was evaluated using a violin plot [26]. If the treatment plans deviated from the protocol, the institutions were required to revise them according to the protocol.

Supplementary analysis of plan complexity

The quality of each treatment plan was evaluated using plan complexity parameters as a supplementary analysis. Only VMAT (which was used by the majority of institutions) was evaluated because the meaning of the plan complexity parameter changes depending on the beam-delivery technique. The plan complexity parameters included the modulated complexity score for VMAT (MCS_v), average aperture area (AA), and monitor unit (MU) [27, 28].

Results

Table 2 presents details of the planning information. TrueBeam and TrueBeam STx (Varian Medical Systems, Palo, Alto, CA, USA) represent the treatment machines to be used in most of the institutions. The Eclipse software (Varian Medical Systems) was used in 58.5% (24/41) of the institutions for treatment planning. Acuros XB

Table 1 Dose and dose-volume criteria for PTV and oars for arms A and B

Structure	Dose-volume criteria	Arm A		Arm B	
		Per protocol	Acceptable variation	Per protocol	Acceptable variation
PTV	$V_{90\%}$	≥ 98%	≥ 95%	≥ 98%	≥ 95%
	$D_{50\%}$	98% ≤, ≤ 102%	95% ≤, ≤ 105%	98% ≤, ≤ 102%	95% ≤, ≤ 105%
	$D_{2\%}$	≤ 107%	≤ 110%	≤ 107%	≤ 110%
Retina_L or Retina_R	$D_{2\%}$	≤ 39.0 Gy	-	≤ 25.4 Gy	-
Brain Stem	$D_{33.3\%}$	≤ 46.8 Gy	-	≤ 30.0 Gy	-
	$D_{66.7\%}$	≤ 43.3 Gy	-	≤ 27.9 Gy	-
	$D_{98\%}$	≤ 41.7 Gy	-	≤ 27.0 Gy	-
Spinal Cord	$D_{2\%}$	≤ 41.7 Gy	-	≤ 27.0 Gy	-
Cerebrum	$D_{33.3\%}$	≤ 46.8 Gy	-	≤ 30.0 Gy	-
	$D_{66.7\%}$	≤ 43.8 Gy	-	≤ 28.2 Gy	-
Optic Nerve_L or Optic Nerve_R	$D_{2\%}$	≤ 43.8 Gy	-	≤ 28.2 Gy	-
Chiasim	$D_{2\%}$	≤ 43.8 Gy	-	≤ 28.2 Gy	-
Lens_L or Lens_R	$D_{2\%}$	< 13.7 Gy	-	< 10.0 Gy	-

PTV, planning target volume; OAR, organ at risk

Table 2 Treatment planning details

Treatment machine		
TrueBeam	9	
TrueBeam STx	7	
Novalis Tx	6	
Clinac iX	3	
Synergy	5	
Trilogy	2	
VersaHD	2	
TomoTherapy	4	
Radixact	3	
Treatment planning system	**Calculation algorithm**	
Eclipse ($n=24$)	AAA	8
	AXB	16
Monaco ($n=3$)	MC	3
Precision ($n=3$)	Convolution-Superposition	3
Planning Station ($n=4$)	Convolution-Superposition	4
Pinnacle ($n=3$)	CCC	2
	Adaptive Convolve	1
RayStation ($n=4$)	CC	4
Beam delivery technique		
VMAT	32	
IMRT	9	
PTV margin [mm]		
3	20	
4	4	
5	17	

VMAT, volumetric modulated arc therapy; IMRT, intensity-modulated radiation therapy; PTV, planning target volume; AAA, Anisotropic Analytical Algorithm; AXB

AcurosXB; MC, Monte Carlo; CCC, Collapsed Cone Convolution; CC, Collapsed Cone

(Varian Medical Systems) was used for the dose calculation algorithm at 39.0% (16/41) of the institutions, and VMAT was used at 78.0% (32/41) of the institutions as the preferred beam-delivery technique. The PTV margins were set at 3, 4, and 5 mm by 20, four and 17 institutions, respectively. Regarding outlining, the research secretariat confirmed that six of the participating institutions did not adhere to the study's protocol, as matters of policy. Table 3 shows further details regarding failed outlining. The GTV was not delineated according to the study protocol in two institutions. The CTV was not delineated according to the protocol, and anatomical barriers were not considered in five institutions. Additionally, inappropriate resection cavity settings were noted for several institutions. One institution modified the PTV by considering both the brain and brainstem, thus, the PTV was not delineated according to the study protocol. Additionally, the target was close to the brainstem in the dummy run case; thus, some of the institutions failed to perform proper outlining. Ultimately, 14.6% (6/41) of the institutions required outlining revisions, and confirmation by the research secretariat provided educational outcomes. Figure 1 shows the outlinings of the 41 institutions. Reference GTVs, CTVs, and PTVs are shown in the context of CT images in Fig. 1(a) and MR images in Fig. 1(b). The full sets of 41 GTV, CTV, and PTV outlinings are shown in Fig. 1(c), (d), and (e), respectively. The means ± standard deviations (SDs) values of the target volumes for GTV, CTV, and PTV were 31.5 ± 28.4 (range, 7.3–107.4) cm^3, 262.8 ± 60.0 (range, 112.7–377.0) cm^3, and 373.9 ± 77.1 (range, 220.3–539.3) cm^3, respectively. Although the same CT and MR images were used to delineate the targets, the GTV and CTV shapes differed at each institution. Compared to the reference outlining, the means ± SDs of the DSC and MDA values were 0.37 ± 0.19 (range, 0.15–0.80) and 9.41 ± 3.99 (range, 2.18–18.11) mm, for GTV; 0.80 ± 0.08 (range, 0.53–0.92) and 4.31 ± 1.85 (range, 1.60–10.60) mm, for CTV; and 0.83 ± 0.05 (range, 0.70–0.93) and 4.2 3 ± 1.45 (range, 1.54–7.57) mm for PTV, respectively. The variation in the GTV structure was particularly large because several institutions included the resection cavity in this parameter. Additionally, PTV outlining varied depending on the institution's margin settings.

Figure 2 shows an example of the dose distribution of arm A for the reference plan (a), as well as plans for the largest (b) and smallest (c) PTVs. All of the institutions created treatment plans based on their delineated targets. Therefore, differences in the dose distributions resulted from these differences in the targets. However, each PTV was surrounded by a 95% dose line, according to the

Table 3 Failed outlining scenarios

	GTV	**CTV**	**PTV**
Institution A	-	Included the resection cavity in the CTV	-
Institution B	-	Did not consider anatomical barriers	-
Institution C	-	No combination of the resection cavity and GTVprimary	-
Institution D	GTV primary outlining was insufficient	Excluded the brainstem from the CTV during outlining	-
Institution E	-	-	Modified the PTV by excluding the brainstem
Institution F	GTV primary outlining was insufficient	No combination of the resection cavity and GTVprimary	-

GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume

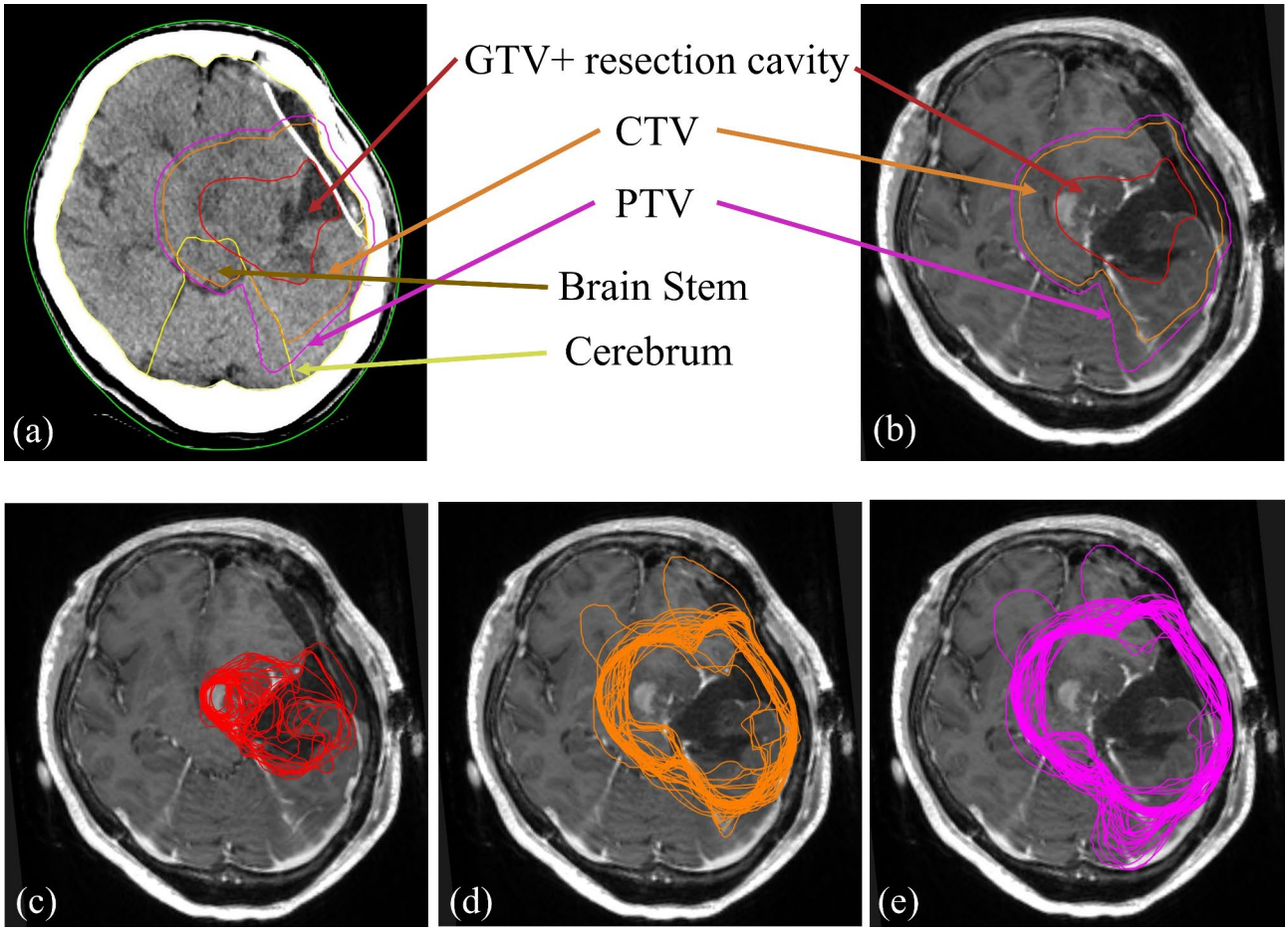

Fig. 1 Reference outlinings of GTV, CTV, and PTV are shown on (**a**) a CT image; and (**b**) an MR image. Outlining of (**c**) GTV, (**d**) CTV, and (**e**) PTV for the 41 participating institutions. Abbreviations: GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; CT, computed tomography; MR, magnetic resonance

study protocol. Figure 3 shows the variations in the dose–volume criteria of the target and OARs for arms A and B of the study. Of the 41 institutions, 40 were within the per-protocol target dose criteria; only one fell within the acceptable limits. In terms of the OAR dose constraints, the dose trends were comparable between arms A and B; however, significant variations were observed in the violin plots depending on the specific OAR. For example, $D_{66.7\%}$ of BrainStem had a large variation because the PTV was close, and the dose depends on the outlining in this case. While a larger variation was observed between Optic Nerve_R vs. Optic Nerve_L, likely because of its proximity to the target volume and its dependence on the volume of the targets.

As a supplementary analysis concerning the complexities of the 32 VMAT plans, their MCS_v, AA, and MU values were 0.29 ± 0.08 (range, 0.16–0.53), $3.82 \pm 0.93 \times 10^3$ (range, 2.63×10^3–6.00×10^3) mm^2, and $6.51 \pm 1.36 \times 10^2$ (range, 3.88×10^3–10.42×10^2) MU for arm A; and 0.31 ± 0.11 (range, 0.17–0.62), $4.04 \pm 1.15 \times 10^3$ (range, 2.62×10^3–6.83×10^3) mm^2, and $11.86 \pm 2.81 \times 10^2$ (range, 7.24×10^2–19.20×10^2) MU for arm B, respectively.

Discussion

This study reports a dummy run of the JCOG1910 study for newly diagnosed glioblastoma using IMRT. A total of 41 enrolled institutions performed outlining and treatment planning. Although variations in outlining were observed across the institutions, all treatment plans were confirmed to be within the protocol for both the A and B study arms. This dummy run is expected to reduce the possibility of deviations in the cases enrolled in the JCOG study by confirming all outlining through the research secretariat and providing feedback to the institutions whenever their outlining failed.

In clinical practice, inter-institutional variability regarding outlining is a topic that merits consideration. Cattaneo et al. reported inter-observer variability for brain gliomas [29]. Five physicians outlined the CTVs for seven patients with gliomas and observed that their concordance index varied between 21% and 72%. However,

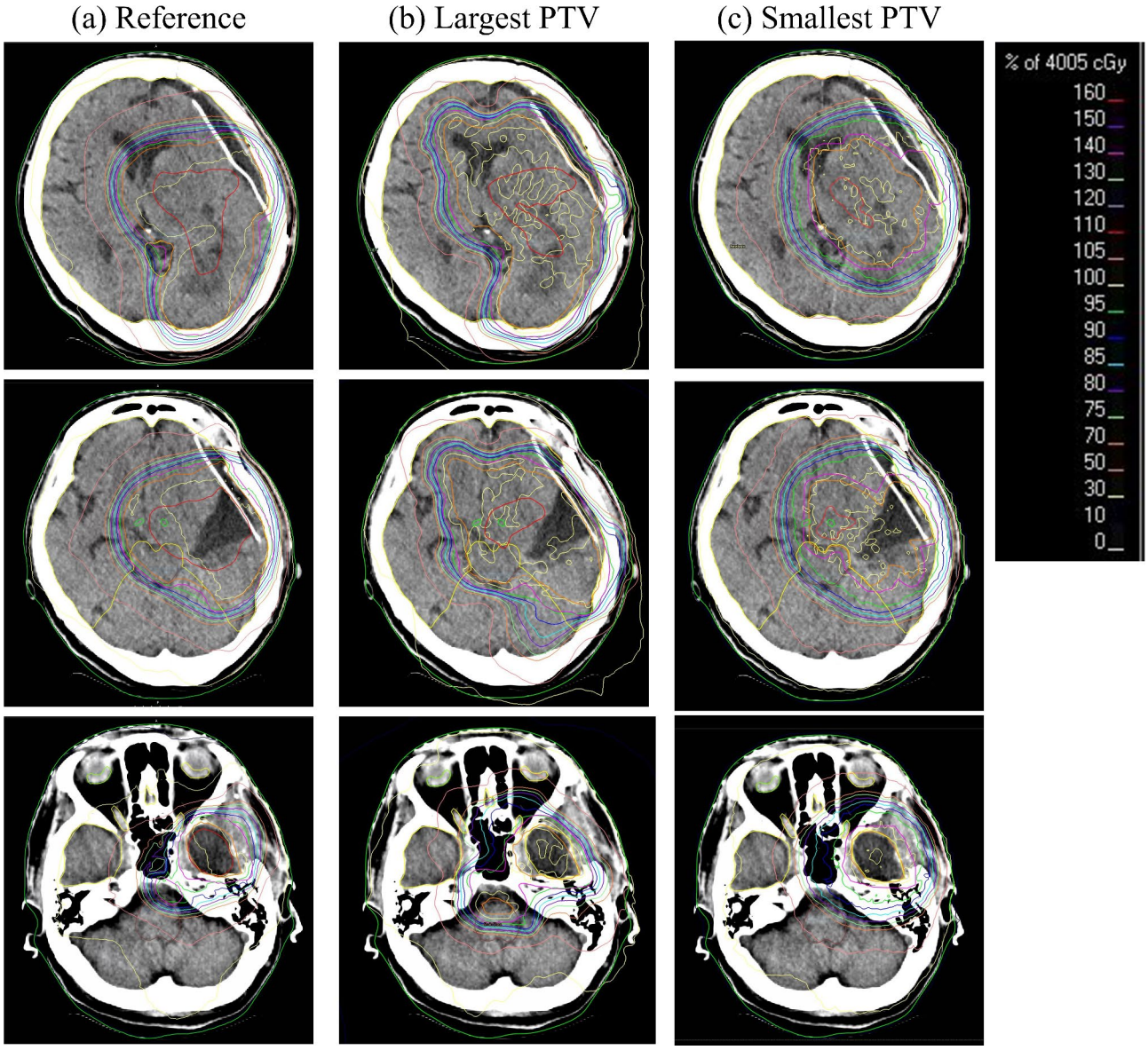

Fig. 2 Examples of dose distributions in arm A of (**a**) the reference plan, (**b**) the plan for the largest PTV, and (**c**) the plan for the smallest PTV. Abbreviation: PTV, planning target volume

they also concluded that the use of CT and MRI reduced the inter-observer variability in target volume outlining for postoperative irradiation. In the current study, 41 institutions delineated target volumes for gliomas based on CT and MR images. In our DSC and MDA evaluations, although the GTV outlining varied between institutions, the CTV outlinings were comparable to the reference CTV, suggesting that outlining was feasible according to the study protocol. Additionally, the outlining of targets is closely related to the incidence of radiation injury [30]; therefore, this dummy run is expected to standardize the outlining capabilities across different institutions.

Similarly, the quality of treatment plans can vary between institutions. Musat et al. evaluated dosimetric parameters and reported on the quality of treatment planning in the EORTC low-grade glioma trial 22,033–26,033 [16]. Their dummy run involving 40 institutions and 41 plans permitted 3D-CRT and IMRT, with a prescribed dose of 50.4 Gy in 1.8 Gy per fraction. The dose distributions were satisfactory, with mean values of 1.5 for the RTOG conformity index and 1.0 for the coverage factor, indicating that most of the participating institutions adhered to the study protocol's requirements. Abrunhosa-Branquinho et al. reported retrospective individual case reviews of QA treatment in their RTOG 0834 intergroup trial [31]. Their trial was designed to

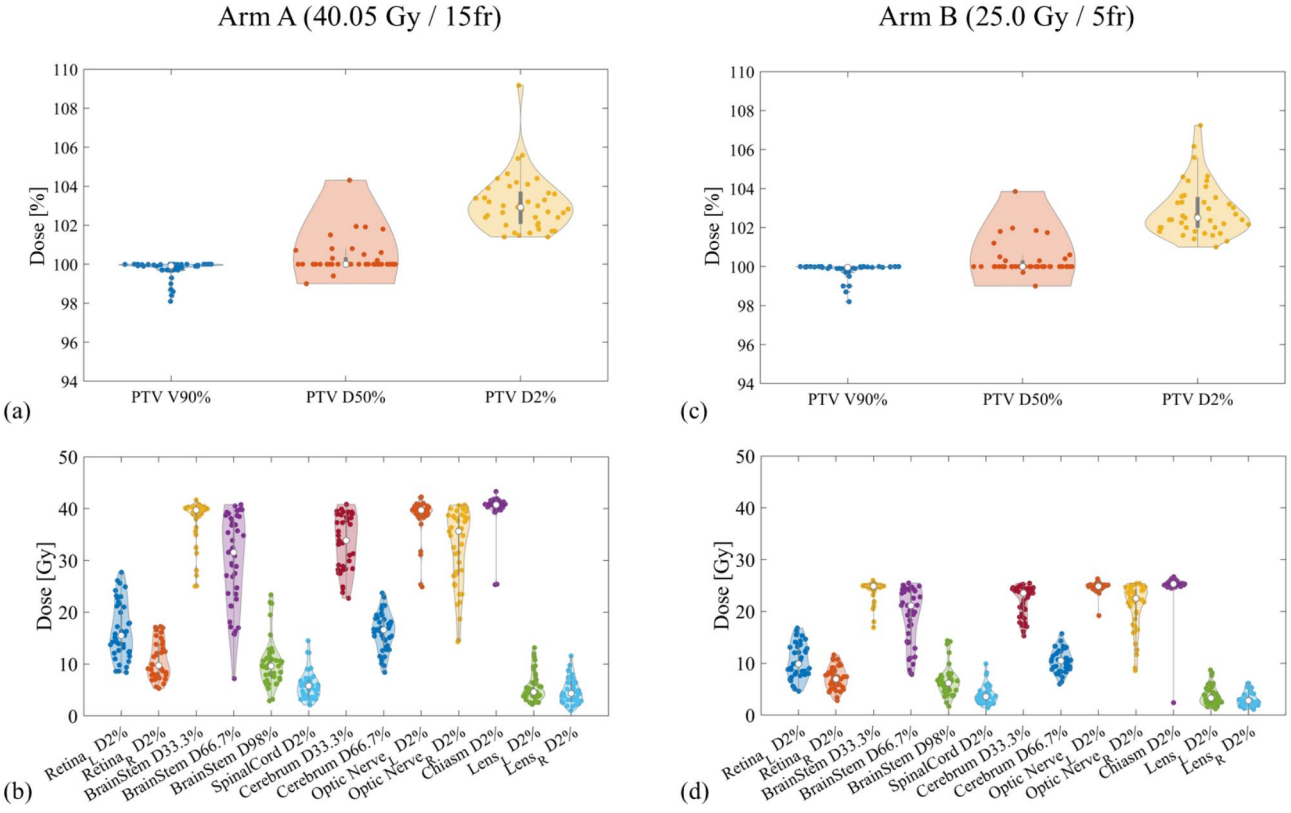

Fig. 3 Violin plots of dose-volume parameters of the targets and OARs for arms **A** and **B**. Abbreviation: OARs, organs at risk

evaluate the effect of concurrent and adjuvant temozolomide chemotherapy on newly diagnosed non-1p/19q deleted anaplastic gliomas and allowed the use of 3D-CRT and IMRT for treatment planning. Sixty-nine institutions participated, and 62 cases were evaluated. Of these, 22 were assessed as being per protocol (35.5%), 11 were considered acceptable variations (17.7%), and 29 were unacceptable (46.8%). Therefore, the authors concluded that radiotherapy trials should include individual case reviews. Of the 41 institutions that participated in this study, six were deemed as not having followed the protocol for outlining; however, they later revised their delineations to levels deemed acceptable by the research secretariat. We also confirmed that both the study arms were as per protocol in terms of using IMRT or VMAT techniques. Thus, this dummy run study is expected to reduce the number of unacceptable cases in the upcoming main clinical trials.

Treatment plan complexity was evaluated for VMAT plans in the supplementary analysis. As a multi-institutional verification, Desai et al. assessed the plan complexity characteristic using four standardized Imaging and Radiation Oncology Core phantoms [32] for 1,723 plans (VMAT, $n = 1{,}110$; step-and-shoot IMRT, $n = 187$; sliding-window IMRT, $n = 426$). They found a substantial variability in plan complexity between institutions that planned for the same object. Similarly, Okamoto et al. investigated plan complexity parameters for 210 plans involved in a head-and-neck VMAT competition [33]. They reported considerable variability in planning skills between planners. Although plan complexity evaluation is not required for the QA program in the JCOG1910 study, it was noted that the treatment plan quality may vary between institutions even if the same beam-delivery technique is used.

Nonetheless, we acknowledge that this study has some limitations. Variations were observed in the outlining between the institutions, even when the same case was used. Additionally, some cases of failed outlining (judged by the study protocol) were observed. Thus, outlining and treatment plans should be reviewed to ensure quality for individual case reviews during prospective studies.

Conclusions

Treatment planning dose distributions fell within the study protocol's guidelines for both the A and B study arms; however, this dummy-run study revealed notable variations in outlining. Therefore, it is necessary that appropriate feedback and periodic information sharing with participating institutions is implemented in the upcoming prospective JCOG1910 study.

Abbreviations

RTSG	Radiation Therapy Study Group
JCOG	Japan Clinical Oncology Group
3D-CRT	Three-dimensional conformal radiotherapy
IMRT	Intensity-modulated radiation therapy
VMAT	Volumetric modulated arc therapy
MPWG	Medical Physics Working Group
QA	Quality assurance
CT	Computed tomography
MR	Magnetic resonance
FLAIR	Fluid-attenuated inversion recovery
CE	Contrast-enhanced
OARs	Organs at risk
GTV	Gross tumor volume
CTV	Clinical target volume
PTV	Planning target volume
ICRU	International Commission on Radiation Units and Measurements
DSC	Dice similarity coefficient
MDA	Mean distance agreement
MCSv	Modulated complexity score for VMAT
AA	Average aperture area
MU	Monitor unit
SD	Standard deviation

Acknowledgements
We thank all members of the JCOG Data Center/Operation Office, the Brain Tumor Study Group, and the Radiation Therapy Study Group of the Japan Clinical Oncology Group.

Author contributions
T.O., M.U, Y.M., Y.A. and T.M. contributed to the study concept and design. T.O. and M.U. wrote the initial draft of the main manuscript. Y.M., Y.A., M.N., N. T., H.I., K. N., S. I., Y. N. and T.M. assisted in manuscript preparation. All authors critically revised the manuscript for intellectual content and approved the final manuscript.

Funding
This study was supported by the Japanese National Cancer Center Research and Development Fund (2020-J-3 and 2023-J-3) and the Japan Agency for Medical Research and Development (AMED; JP20ck0106619).

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

Declarations

Ethics approval and consent to participate
This study is being conducted in accordance with the principles expressed in the Declaration of Helsinki, Clinical Trials Act (Act No. 16 of April 14, 2017) and SPRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. The protocol for this study was approved by the JCOG Protocol Review Committee on April 24, 2020, and by the National Cancer Center Hospital Certified Review Board on June 25, 2020 (CRB3180008). Written informed consent has been obtained from all enrolled participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Radiation Oncology, Shiga General Hospital, Shiga, Japan
[2]Department of Radiation Oncology and Image-Applied Therapy, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[3]Department of Neurosurgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[4]Department of Advanced Medical Physics, Graduate School of Medicine, Kyoto University, Kyoto, Japan
[5]Medical Physics Laboratory, Division of Health Science, Graduate School of Medicine, Osaka University, Osaka, Japan
[6]Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan
[7]Department of Radiation Oncology, Osaka Medical and Pharmaceutical University, Osaka, Japan
[8]Department of Radiation Oncology, St. Luke's International Hospital, St. Luke's International University, Tokyo, Japan
[9]Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, Tokyo, Japan

Received: 2 October 2024 / Accepted: 23 February 2025
Published online: 09 March 2025

References

1. Malmstrom A, Gronberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the nordic randomised, phase 3 trial. Lancet Oncol. 2012;13:916–26. https://doi.org/10.1016/S1470-2045(12)70265-6.
2. Guedes de Castro D, Matiello J, Roa W, Ghosh S, Kepka L, Kumar N, et al. Survival outcomes with Short-Course radiation therapy in elderly patients with glioblastoma: data from a randomized phase 3 trial. Int J Radiat Oncol Biol Phys. 2017;98:931–38. https://doi.org/10.1016/j.ijrobp.2017.03.037.
3. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant Temozolomide for glioblastoma. N Engl J Med. 2005;352:987–96. https://doi.org/10.1056/NEJMoa043330.
4. Wakabayashi T, Natsume A, Mizusawa J, Katayama H, Fukuda H, Sumi M, et al. JCOG0911 INTEGRA study: a randomized screening phase II trial of interferonbeta plus Temozolomide in comparison with Temozolomide alone for newly diagnosed glioblastoma. J Neurooncol. 2018;138:627–36. https://doi.org/10.1007/s11060-018-2831-7.
5. Kadota T, Saito R, Kumabe T, Mizusawa J, Katayama H, Sumi M, et al. A multicenter randomized phase III study for newly diagnosed maximally resected glioblastoma comparing carmustine wafer implantation followed by chemoradiotherapy with Temozolomide with chemoradiotherapy alone; Japan clinical oncology group study JCOG1703 (MACS study). Jpn J Clin Oncol. 2019;49:1172–75. https://doi.org/10.1093/jjco/hyz169.
6. Brandes AA, Franceschi E, Tosoni A, Benevento F, Scopece L, Mazzocchi V, et al. Temozolomide concomitant and adjuvant to radiotherapy in elderly patients with glioblastoma: correlation with MGMT promoter methylation status. Cancer. 2009;115:3512–8. https://doi.org/10.1002/cncr.24406.
7. Fiorica F, Berretta M, Colosimo C, Stefanelli A, Ursino S, Zanet E, et al. Glioblastoma in elderly patients: safety and efficacy of adjuvant radiotherapy with concomitant Temozolomide. Arch Gerontol Geriatr. 2010;51:31–5. https://doi.org/10.1016/j.archger.2009.06.011.
8. Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol. 2004;22:1583–8. https://doi.org/10.1200/JCO.2004.06.082.
9. Roa W, Kepka L, Kumar N, Sinaika V, Matiello J, Lomidze D, et al. International atomic energy agency randomized phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme. J Clin Oncol. 2015;33:4145–50. https://doi.org/10.1200/JCO.2015.62.6606.
10. Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, et al. Short-Course radiation plus Temozolomide in elderly patients with glioblastoma. N Engl J Med. 2017;376:1027–37. https://doi.org/10.1056/NEJMoa1611977.
11. Arakawa Y, Sasaki K, Mineharu Y, Uto M, Mizowaki T, Mizusawa J, et al. A randomized phase III study of short-course radiotherapy combined with Temozolomide in elderly patients with newly diagnosed glioblastoma; Japan clinical oncology group study JCOG1910 (AgedGlio-PIII). BMC Cancer. 2021;21:1105. https://doi.org/10.1186/s12885-021-08834-0.
12. Nakamura M, Zhou D, Minemura T, Kito S, Okamoto H, Tohyama N, et al. A virtual audit system for intensity-modulated radiation therapy credentialing in Japan clinical oncology group clinical trials: A pilot study. J Appl Clin Med Phys. 2023;24:e14040. https://doi.org/10.1002/acm2.14040.
13. Pettersen MN, Aird E, Olsen DR. Quality assurance of dosimetry and the impact on sample size in randomized clinical trials. Radiother Oncol. 2008;86:195–9. https://doi.org/10.1016/j.radonc.2007.07.001.

14. Brooks C, Miles E, Hoskin PJ. Radiotherapy trial quality assurance processes: a systematic review. Lancet Oncol. 2024;25:e104–13. https://doi.org/10.1016/S1470-2045(23)00625-3.
15. Weber DC, Tomsej M, Melidis C, Hurkmans CW. QA makes a clinical trial stronger: evidence-based medicine in radiation therapy. Radiother Oncol. 2012;105:4–8. https://doi.org/10.1016/j.radonc.2012.08.008.
16. Musat E, Roelofs E, Bar-Deroma R, Fenton P, Gulyban A, Collette L, et al. Dummy run and conformity indices in the ongoing EORTC low-grade glioma trial 22033–26033: first evaluation of quality of radiotherapy planning. Radiother Oncol. 2010;95:218–24. https://doi.org/10.1016/j.radonc.2010.03.005.
17. Okamoto H, Murakami N, Isohashi F, Kasamatsu T, Hasumi Y, Kobayashi H, et al. Plan quality association between dummy run and individual case review in a prospective multi-institutional clinical trial of postoperative cervical cancer patients treated with intensity-modulated radiotherapy: Japan clinical oncology group study (JCOG1402). Radiother Oncol. 2023;183:109630. https://doi.org/10.1016/j.radonc.2023.109630.
18. Matzinger O, Poortmans P, Giraud JY, Maingon P, Budiharto T, van den Bergh AC, et al. Quality assurance in the 22991 EORTC ROG trial in localized prostate cancer: dummy run and individual case review. Radiother Oncol. 2009;90:285–90. https://doi.org/10.1016/j.radonc.2008.10.022.
19. Davis JB, Reiner B, Dusserre A, Giraud JY, Bolla M. Eortc. Quality assurance of the EORTC trial 22911. A phase III study of post-operative external radiotherapy in pathological stage T3N0 prostatic carcinoma: the dummy run. Radiother Oncol. 2002;64:65–73. https://doi.org/10.1016/s0167-8140(02)00143-3.
20. The International Commission on Radiation Units and Measurements. J ICRU. 2010;10. https://doi.org/10.1093/jicru/ndq001. NP.2-NP.
21. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991;21:109–22. https://doi.org/10.1016/0360-3016(91)90171-y.
22. 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.
23. Knoos T, Wieslander E, Cozzi L, Brink C, Fogliata A, Albers D, et al. Comparison of dose calculation algorithms for treatment planning in external photon beam therapy for clinical situations. Phys Med Biol. 2006;51:5785–807. https://doi.org/10.1088/0031-9155/51/22/005.
24. Vassiliev ON, Wareing TA, McGhee J, Failla G, Salehpour MR, Mourtada F. Validation of a new grid-based Boltzmann equation solver for dose calculation in radiotherapy with photon beams. Phys Med Biol. 2010;55:581–98. https://doi.org/10.1088/0031-9155/55/3/002.
25. Richmond N, Angerud A, Tamm F, Allen V. Comparison of the raystation photon Monte Carlo dose calculation algorithm against measured data under homogeneous and heterogeneous irradiation geometries. Phys Med. 2021;82:87–99. https://doi.org/10.1016/j.ejmp.2021.02.002.
26. Hintze JL, Nelson RD. Violin plots: A box Plot-Density trace synergism. Am Stat. 1998;52. https://doi.org/10.1080/00031305.1998.10480559.
27. Masi L, Doro R, Favuzza V, Cipressi S, Livi L. Impact of plan parameters on the dosimetric accuracy of volumetric modulated Arc therapy. Med Phys. 2013;40:071718. https://doi.org/10.1118/1.4810969.
28. Ono T, Hirashima H, Iramina H, Mukumoto N, Miyabe Y, Nakamura M, et al. Prediction of dosimetric accuracy for VMAT plans using plan complexity parameters via machine learning. Med Phys. 2019;46:3823–32. https://doi.org/10.1002/mp.13669.
29. Cattaneo GM, Reni M, Rizzo G, Castellone P, Ceresoli GL, Cozzarini C, et al. Target delineation in post-operative radiotherapy of brain gliomas: interobserver variability and impact of image registration of MR(pre-operative) images on treatment planning CT scans. Radiother Oncol. 2005;75:217–23. https://doi.org/10.1016/j.radonc.2005.03.012.
30. Swennen MH, Bromberg JE, Witkamp TD, Terhaard CH, Postma TJ, Taphoorn MJ. Delayed radiation toxicity after focal or whole brain radiotherapy for low-grade glioma. J Neurooncol. 2004;66:333–9. https://doi.org/10.1023/b:neon.0000014518.16481.7e.
31. Abrunhosa-Branquinho AN, Bar-Deroma R, Collette S, Clementel E, Liu Y, Hurkmans CW, et al. Radiotherapy quality assurance for the RTOG 0834/EORTC 26053– 22054/NCIC CTG CEC.1/CATNON intergroup trial concurrent and adjuvant Temozolomide chemotherapy in newly diagnosed non-1p/19q deleted anaplastic glioma: individual case review analysis. Radiother Oncol. 2018;127:292–98. https://doi.org/10.1016/j.radonc.2018.03.013.
32. Desai V, Labby Z, Culberson W, DeWerd L, Kry S. Multi-institution single geometry plan complexity characteristics based on IROC phantoms. Med Phys. 2024;51:5693–707. https://doi.org/10.1002/mp.17086.
33. Okamoto H, Wakita A, Tani K, Kito S, Kurooka M, Kodama T, et al. Plan complexity metrics for head and neck VMAT competition plans. Med Dosim. 2024. https://doi.org/10.1016/j.meddos.2024.01.007.

Publisher's note