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Hypofractionated stereotactic radiotherapy for large brain metastases: optimizing the dosimetric parameters

Radiothérapie stéréotaxique hypofractionnée des métastases cérébrales volumineuses : optimisation de la dosimétrie

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Running title: Brain stereotactic radiotherapy

SUMMARY

Purpose: Stereotactic radiotherapy plays a major role in the treatment of brain metastases (BM). We aimed to compare the dosimetric results of four plans for hypofractionated stereotactic radiotherapy (HFSRT) for large brain metastases.

Material and Methods: Ten patients treated with upfront NovalisTx® non-coplanar multiple dynamic conformal arcs (DCA) HFSRT for ≥ 25 mm diameter single BM were included. Three other volumetric modulated arc therapy (VMAT) treatment plans were evaluated: with coplanar arcs (Eclipse®, Varian, VMAT_CEclipse®), with coplanar and non-coplanar arcs (VMAT_{nc}Eclipse®), and with non-coplanar arcs (Elements Cranial SRS®, Brainlab, VMAT_{nc}Elements®). The marginal dose prescribed for the PTV was 23.1 Gy (isodose 70%) in three fractions. The mean GTV was 27 mm³.

Results: Better conformity indices were found with all VMAT techniques compared to DCA (1.05 vs 1.28, $p < 0.05$). Better gradient indices were found with VMAT_{nc}Elements® and DCA (2.43 vs 3.02, $p < 0.001$). High-dose delivery in healthy brain was lower with all VMAT techniques compared to DCA (5.6 to 6.3 cc vs 9.4 cc, $p < 0.001$). Low-dose delivery (V5Gy) was lower with VMAT_{nc}Eclipse® or VMAT_{nc}Elements® than with DCA (81 or 94 cc vs 110 cc, $p = 0.02$).

Conclusions: NovalisTx® VMAT HFSRT for ≥ 25 mm diameter brain metastases provides the best dosimetric compromise in terms of target coverage, sparing of healthy brain tissue and low-dose delivery compared to DCA.

Keywords: brain metastasis, stereotactic radiotherapy, dosimetry, VMAT, NovalisTx®

SUMMARY IN FRENCH

Objectif de l'étude : La radiothérapie stéréotaxique joue un rôle majeur dans le traitement des métastases cérébrales. L'objectif était de comparer les résultats dosimétriques de quatre planifications de radiothérapie stéréotaxique hypofractionnée pour des métastases cérébrales volumineuses.

Matériel et Méthodes : Ont été inclus dix patients traités sur NovalisTx® par irradiation stéréotaxique hypofractionnée en arcthérapie dynamique conformationnelle non coplanaire (ADC) pour une métastase cérébrale ≥ 25 mm. Trois autres plans avec modulation d'intensité volumétrique (RCMI) ont été comparés: avec des arcs coplanaires (Eclipse®, Varian, RCMIncEclipse®), des arcs non coplanaires (Elements Cranial SRS®, Brainlab, RCMIncElements®), et des arcs coplanaires et non coplanaires (RCMIncEclipse®). La dose d'enveloppe était 23,1 Gy (isodose 70%) en trois fractions. Le volume moyen du volume tumoral macroscopique (GTV) était 27 mm³.

Résultats : Les indices de conformité étaient meilleurs pour les RCMI (1,05 contre 1,28, $p < 0,05$). Les indices de gradient étaient meilleurs avec la RCMIncElements® par rapport à l'ADC (2,43 contre 3,02, $p < 0,001$). Moins de fortes doses délivrées dans le parenchyme cérébral sain ont été observées avec les RCMI (5,6 à 6,3 cc contre 9,4 cc, $p < 0,001$). Moins de faibles doses délivrées (V5Gy, volume recevant 5 Gy) ont été observées avec les RCMI non coplanaires par rapport à l'ADC (81 ou 94 cc contre 110 cc, $p = 0,02$).

Conclusion: Les meilleurs résultats dosimétriques de radiothérapie stéréotaxique hypofractionnée en termes de couverture du volume cible et d'épargne du parenchyme cérébral sain à faibles et fortes doses sont obtenus avec les RCMI utilisant des arcs non coplanaires.

Keywords: métastases cérébrales, radiothérapie stéréotaxique, dosimétrie, RCMI, NovalisTx®

Background

Brain metastases are the most common intracranial tumors in adults. Twenty to 40% of cancer patients will develop brain metastases [1–3]. There are different therapeutic possibilities and stereotactic radiotherapy occupies an increasingly important place [4–6]. Local control is similar to that following surgery [7]. Stereotactic radiotherapy aims to deliver a high dose on the target, and it is found that the higher the dose delivered, the lower the risk of recurrence [8]. Conversely, the lower the dose, the lesser the risk of radionecrosis, especially for large brain metastases [9]. In order to limit the appearance of radionecrosis, irradiation of healthy brain parenchyma should be reduced as far as possible. To enable this while maintaining treatment efficiency, hypo-fractionated stereotactic radiotherapy (HFSRT; currently 3 to 5 fractions) is often a solution for large-diameter metastases [10–12]. For LINAC-based HFSRT, non-coplanar multiple dynamic conformal arcs (DCA) have often been used to achieve high conformity while sparing healthy tissues [13]. More recently, volumetric modulated arc therapy (VMAT) has been widely developed [14–16].

The purpose of our study was to compare the dosimetric impact of four different HFSRT techniques for the treatment of large brain metastases (over 25mm in diameter): DCA (Iplan®, Brainlab), VMAT with coplanar arcs (Eclipse®, Varian; VMAT_CEclipse®), VMAT with coplanar and non-coplanar arcs (Eclipse®, Varian; VMAT_{nc}Eclipse®), and VMAT with non-coplanar arcs (Elements®, Brainlab; VMAT_{nc}Elements®). The dosimetric impact was studied in terms of target coverage and the sparing of organs at risk (OAR), especially low and high doses delivered to healthy brain tissues.

Methods

Patients

Ten consecutive patients, treated in our institution with upfront HFSRT between November 2014 and March 2016 for a single brain metastasis with a greatest diameter -of 25 mm or more, were included in this study. Patient and brain metastasis characteristics are detailed in Table 1. The mean brain metastasis largest diameter was 26.6 mm (25-30 mm).

All patients were treated with NovalisTx® equipped with a high definition MultiLeaf Collimator (HD MLC 120) (Varian Medical Systems, Palo Alto, CA, USA and Brainlab, Munich, Germany) using a noninvasive thermoplastic mask plus a localizer box (Brainlab). Positioning of the patients was performed using an ExacTrac® stereoscopic X-ray system (Brainlab) and a robotic couch with six degrees of freedom. Treatments were permitted when the setup error was < 0.7 mm in translation and 0.7° in rotation.

Treatment planning

A planning CT of 1.25-mm thickness was acquired and was matched with the dosimetric MRI sequences of interest using Iplan®, version 4.1 (Brainlab). Three MRI sequences were used : a FLAIR 3D MRI sequence with a 1mm*1mm*1mm voxel size, a T1 3D MPRAGE MRI sequence with contrast agent and a voxel size of 0.8mm*0.8mm*1mm and T1 EG with a 0.6mm*0.6mm*4mm voxel size. The gross tumor volume (GTV) was defined using post Gadolinium contrast-enhanced T1 weighted MRI sequences. The GTV was then extended symmetrically by 2 mm in all dimensions to create the planning target volume (PTV). Mean GTV and PTV were 8.7 cc (5.7-13.6 cc) and 14.5 cc (10.5-21.4 cc) respectively.

The following OARs were contoured: brainstem, eyeballs, lenses, optic nerves, chiasm, cochlea, cranial cavity, and healthy brain (entire cranial cavity – GTV). No margins were around the OARs to create planning OAR volumes (PRVs).

Treatment plans

➤ Non-coplanar dynamic conformal arcs (Iplan®, Brainlab; DCA)

All DCA plans were created with arcs of 6-MV photons. The prescribed dose was 33 Gy at the isocenter and 23.1 Gy (70%) at the PTV envelope in three fractions. Five non-coplanar arcs were used for all patients (Figure 1). The final calculations were performed using Iplan® TPS, version 4.1 (Brainlab), using a pencil-beam algorithm with a spatial resolution of 2.5 mm. This formed a conformational treatment where the leaf positions were adjusted every 10° using Beam Eye View. The collimator was set at zero for all plans.

➤ VMAT (Eclipse®, Varian)

All VMAT plans were created with arcs for 6-MV photons. The prescribed dose was 33 Gy for the GTV and 23.1 Gy (70%) for the PTV. Final calculations were performed using the AAA algorithm on Eclipse® TPS version 13.5 (Varian Medical Systems) [24]. The arc optimization algorithm, the Progressive Resolution Optimizer used in Rapidarc®, optimized leaf position, dose rate, and gantry speed. Optimization parameters with *Normal Tissue Objectives* (NTO) were used to spare healthy tissues and were defined as following: 1) distance from the PTV border (Xstart) = 1 mm, 2) start dose (f0) = target coverage isodose (e.g. 70%), 3) end dose (f∞) = 5% and 4) the fall-off coefficient (k) = 0.3 mm⁻¹. The maximum dose rate was set at 600 MU/min. Couch parameters were also added to the plan to account for attenuation of the mega-voltage beams. VMAT plans followed the

recommendations of the International Commission on Radiation Units and Measurement Report 83.

Coplanar VMAT (VMAT_CEclipse)

The plans were created with two full coplanar arcs (Figure 1). The first arc was planned in a clockwise direction and the second in a counter-clockwise direction. For all the plans, the collimator was rotated to 30° for the first arc and to 330° for the second arc to reduce the tongue-and-groove effect.

Coplanar and Non-coplanar VMAT (VMAT_{Tn}C_{Eclipse})

The plans were created with one full coplanar arc and 3 partial non-coplanar arcs spaced by 45° (Figure 1). The maximum arc rotation amplitude was 160°. The rotation of the collimator was 10°, 350°, 350°, 350° and 10° for the first, second, third and fourth arcs respectively.

➤ VMAT (Elements Cranial SRS®, Brainlab; VMAT_{Tn}C_{Elements})

The prescribed dose was 33 Gy at the isocenter and 23.1 Gy (70%) at the PTV envelope in three fractions. Plans were generated using the 4Pi optimization algorithm on Elements Cranial SRS® (Brainlab). Optimal placement of non-coplanar arcs (Figure 1), gantry starting and stopping, optimized leaf position, dose rate, and gantry speed were automatically generated. The maximum dose rate was set at 600 MU/min. Couch parameters were also added to the plan to account for attenuation of the mega-voltage beams.

Statistical analysis

The plan analyses were based on dose-volume histogram (DVH) data. For target volume coverage, V70% (23.1Gy), mean dose (D_{mean}) to the GTV and PTV were noted. For healthy brain high and low-dose delivery, V23.1Gy, V20Gy, V18Gy were used and low doses with

V10Gy and V5Gy. We also calculated two indexes for the PTV: the inverse Paddick conformity index (CI) and the gradient index (GI).

The inverse Paddick CI is defined as follows:

$$CI = \frac{(Total\ volume\ receiving \geq D_{coverage})}{(PTV\ volume\ receiving \geq D_{coverage})} * \frac{(PTV\ volume)}{(PTV\ volume\ receiving \geq D_{coverage})}$$

A value of 1 is the ideal case. The larger the value, the less conformal is the treatment.

The GI is defined as follows:

$$GI = \frac{(Total\ volume\ receiving \geq 50\% D_{coverage})}{(Total\ volume\ receiving \geq 100\% D_{coverage})}$$

The GI describes the steepness of the dose fall-off from the 23.1 Gy isodose ($D_{coverage}$ in our case) to the 11.55 isodose (50% of $D_{coverage}$). The larger the value, the shallower is the gradient.

Statistical analyses were performed using R v2.15.1 (<http://www.cran.r-project.org>). To explore changes across the four sets of data obtained (DCA, VMAT_{cEclipse}, VMAT_{nEclipse} and VMAT_{nElements}), Kruskal-Wallis tests were performed, followed by Dunn tests for pairwise comparisons. If the associated p-value was under the significance level ($\alpha=0.05$), it was assumed that there was a statistically significant difference between the data sets compared.

Results

All dosimetric results are presented in Table 2.

➤ *Target volume coverage*

For all four plans, the mean PTV coverage with the 23.1Gy (V70%) isodose was over 99%. Mean CIs were significantly lower with all VMAT techniques vs DCA (1.28, 1.04, 1.05 and 1.07 for DCA, VMAT_CEclipse, VMAT_{Tnc}Eclipse, VMAT_{Tnc}Elements respectively; p<0.05). Mean GIs were significantly lower with VMAT_{Tnc}Elements and DCA vs VMAT_CEclipse and VMAT_{Tnc}Eclipse (p<0.001). There were no significant differences between Dmeans to the GTV or PTV between the different techniques.

➤ *Healthy brain*

Table 2 shows all HDV results for the healthy brain (entire cranial cavity – GTV). Mean V23.1Gy were significantly lower for all VMAT techniques vs DCA (9.35cc, 5.9 cc, 5.6 cc and 6.3cc for DCA, VMAT_CEclipse, VMAT_{Tnc}Eclipse, VMAT_{Tnc}Elements respectively; p<0.001). Mean V18Gy were significantly lower for all VMAT techniques vs DCA (15.5cc, 12.2 cc, 10.9 cc and 11.3cc for DCA, VMAT_CEclipse, VMAT_{Tnc}Eclipse, VMAT_{Tnc}Elements respectively; p=0.04).

➤ *Low-dose delivery*

For DCA, VMAT_CEclipse, VMAT_{Tnc}Eclipse and VMAT_{Tnc}Elements, mean V5Gy were 109.7 cc, 146.4 cc, 82 cc and 94 cc respectively (p<0.05 VMAT_{Tnc} vs VMAT_CEclipse and DCA); mean V10Gy were 40.1 cc, 45.3 cc, 30.0 cc and 32.6 cc respectively (ns).

Discussion

The aim of our study was to optimize the dosimetric parameters of HFSRT for treatment of large brain metastases (>25 mm diameter), especially concerning predictive factors of radionecrosis. Several authors have demonstrated the link between the volume of brain receiving a specific isodose and the risk of radionecrosis [17], particularly with the volume of high-dose irradiated healthy brain [18–20]. In the context of single fraction radiosurgery, Minniti et al. found that $V_{12\text{Gy}} > 10.9$ cc corresponded to a 47% risk of developing radionecrosis [21]. Other authors found similar outcomes with $V_{12\text{Gy}}$ [18]. As far as HFSRT is concerned, little data is available. Minniti et al. found that for brain metastasis treated with three-fraction HFSRT, the 1-year risk of radionecrosis was up to 24% for $V_{18\text{Gy}} > 30.2$ cc, and up to 14 % for $V_{21\text{Gy}} > 20.9$ cc [22,23]. Inoue et al. found that for brain metastasis treated with three-fraction HFSRT, a $V_{23\text{Gy}}$ over 7cc was a significant predictive factor of radionecrosis [24]. Interestingly, in our study, the mean $V_{23.1\text{Gy}}$ was 9.4 cc for DCA and was reduced to 5.6-6.3 cc (i.e. about 36% reduction) with VMAT techniques, and mean $V_{18\text{Gy}}$ was reduced from 15.5 cc to 10.9-12.2 cc (i.e. about 25% reduction). According to literature, these reductions may be clinically important. The benefits of VMAT on dose distribution have already been demonstrated in several intracranial stereotactic studies for the treatment of vestibular schwannomas [25] or meningiomas of the skull base [26].

In this study, we paid particular attention to dosimetric parameters relating to predictive factors of radionecrosis described in the literature. Radionecrosis incidence ranges from 2 to 22% for radiological radionecrosis and 1 to 14% for symptomatic radionecrosis (15–17). Radionecrosis appears within 3 years in 80% of cases [29] traditionally 6-12 months after stereotactic radiotherapy. Differentiation between progressive recovery and radionecrosis is difficult. The definition of radionecrosis is histological and corresponds to the appearance of cerebral vascular lesions secondary to irradiation resulting in ischemic injury, possible

hemorrhage and in severe cases white matter demyelination. [30]. Apart from high-dose healthy brain irradiation discussed above, other predictive factors for radionecrosis have been identified: CI [31], total dose [32,33], fractionation [33], number of isocenters [34], previous radiotherapy [35], infratentorial location of the BM [36] and concomitant chemotherapy [33]. Concerning CI, we found that all VMAT plans gave excellent results between 1.04 and 1.07, vs 1.27 for DCA ($p < 0.001$).

Concerning the different VMAT techniques that we studied, although they all yielded acceptable dosimetric results, some differences can be noted. We found that VMAT including non-coplanar arcs provided the best dosimetric compromise in terms of target coverage, sparing of healthy brain tissue and low-dose delivery. Even if treatment time is longer, in our institution we favor the use of multiple non-coplanar arcs because they enable the reduction of low-dose delivery over coplanar arcs only. This could be of ~~clinical~~ clinical interest, especially in case of regional brain recurrence requiring new stereotactic irradiation, which is often the case with ~~upfront~~ HFSRT. Indeed, in case of repeated treatments, this may lower the cumulative dose to the healthy brain, even if, up-to-date it has not been proven that it might have a clinical impact. In our study, VMATnc_{Eclipse} and VMATnc_{Elements} provided similar dosimetric results except for GI which was significantly better for VMATnc_{Elements}. For this reason, we now favor the use of VMATnc_{Elements}, especially since, in daily routine practice, the computing time to generate the dosimetry is almost instantaneous for VMATnc_{Elements} and can take several dozen minutes for VMATnc_{Eclipse} (using the AAA algorithm on Eclipse® TPS version 13.5).

Conclusions

The use of VMAT with non-coplanar arcs for HFSRT in the treatment of large brain metastases provides excellent dosimetric results in terms of target coverage, sparing of

healthy brain and low-dose delivery. We found that V23.1Gy and V18Gy were reduced by 36% and 25% respectively, which may be clinically important concerning the risk of radionecrosis. We found that Eclipse® and Elements Cranial SRS® provided similar dosimetric results, with a better GI for Elements Cranial SRS®.

List of abbreviations

CI: Conformity Index

DCA: Dynamic Conformal Arcs

Dmean: Mean Dose

DVH: Dose-Volume Histogram

GI: Gradient Index

GTV: Gross Tumor Volume

HFSRT: Hypo-Fractionated Stereotactic Radiotherapy

NTO: Normal Tissue Objectives

OAR: Organ At Risk

PRV: Planning OAR Volume

PTV: Planning Target Volume

VMAT: Volumetric Modulated Arc Therapy

VMAT_{C_{Eclipse}} : VMAT with coplanar arcs (Eclipse®, Varian)

VMATn_{C_{Eclipse}} : VMAT with coplanar and non-coplanar arcs (Eclipse®, Varian)

VMATn_{C_{Elements}} : VMAT with non-coplanar arcs (Elements Cranial SRS®, Brainlab)

Declarations

Ethics approval and consent to participate

This work did not require any written patient consent. The local ethics committee of Centre Jean Perrin approved this work.

Consent for publication

Not applicable

Availability of data and material

The datasets supporting the conclusions of this article are included in the article.

Competing interests

JB had speaker honoraria from Brainlab. The remaining authors declare that they have no competing interests.

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Not applicable

Authors' contributions

LB designed the study, collected the data and wrote the manuscript. VC and VD participated in the study design and interpretation and performed treatment plan analyses. EC performed the statistical analyses and participated in interpretation. JM, PV, TK and ML participated in the study design and interpretation. JB designed the study, participated in interpretation of the data and wrote the manuscript. GD was also in charge of data analysis, manuscript writing and editing. All authors read and approved the final manuscript.

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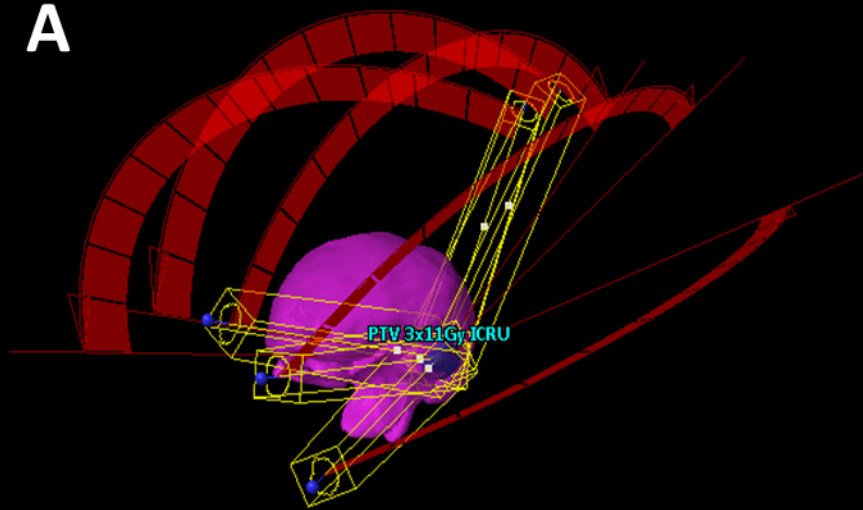
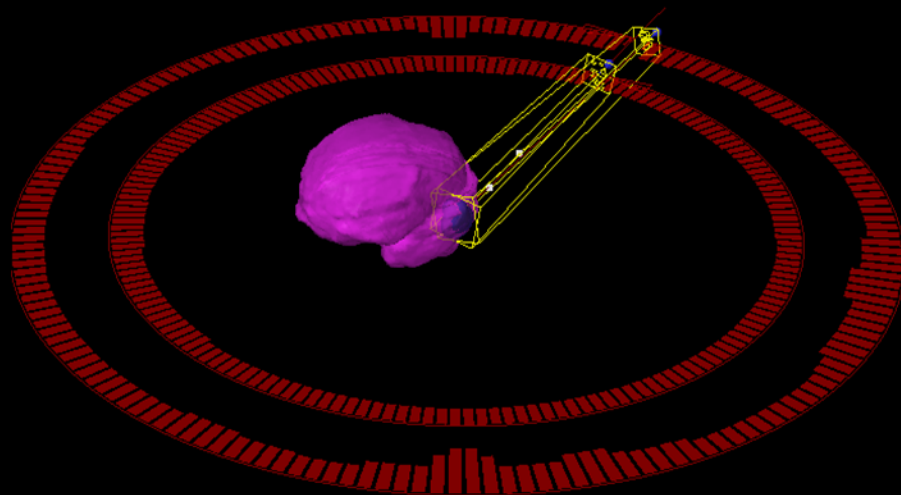
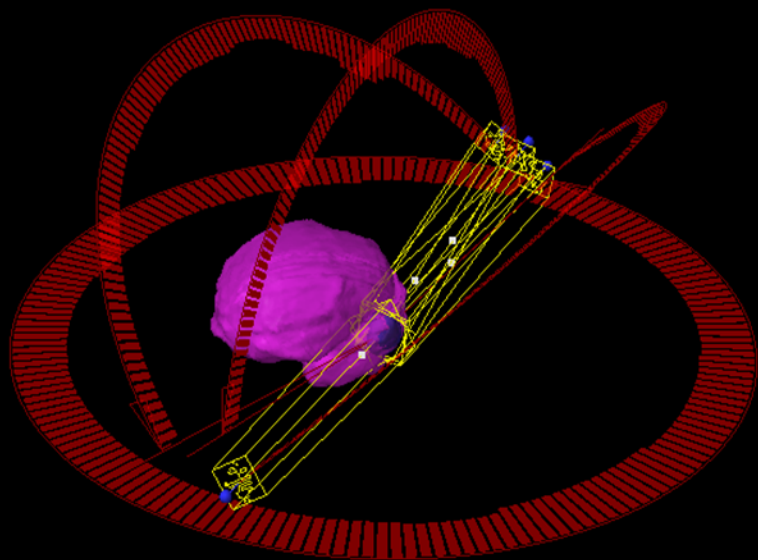
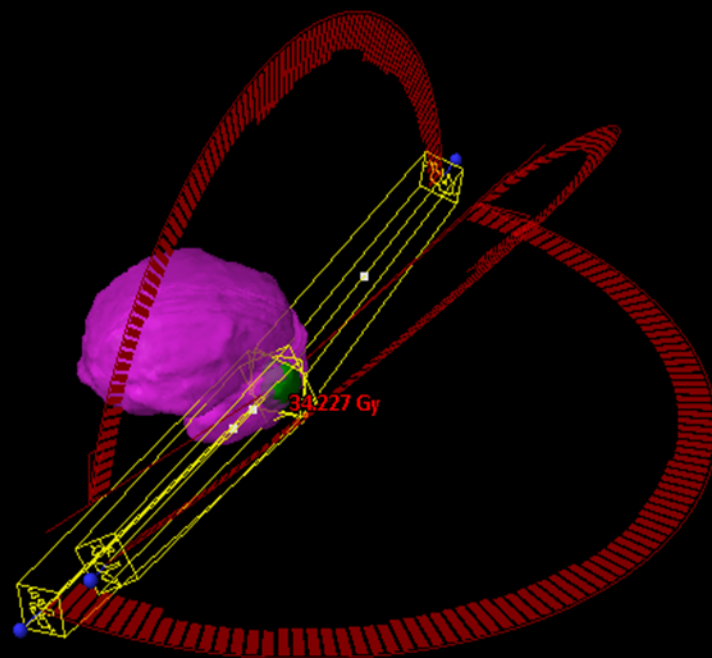
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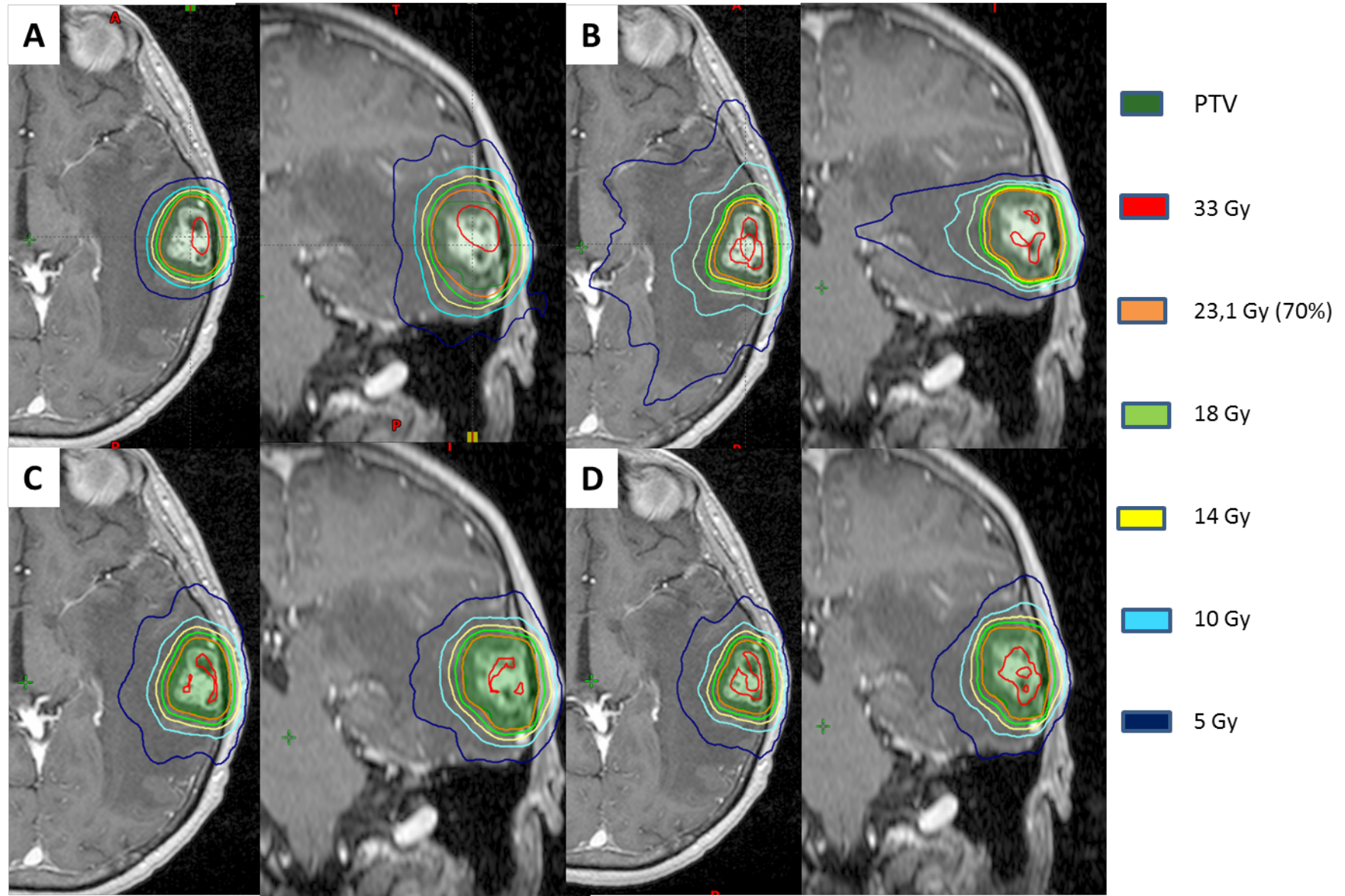
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A**B****C****D**



Patient	Age	Site of the primitive tumour	GTV largest diameter (mm)	GTV volume (cc)	PTV volume (cc)	Brain metastasis localization
1	71	Lung	26	11.6	19.0	Cerebellum
2	56	Anal canal	26	7.3	12.4	Parietal
3	81	Kidney	28	6.8	12.2	Temporal
4	74	Melanoma	25	5.7	10.5	Parietal
5	65	Kidney	26	6.3	11.1	Temporal
6	68	Lung	25	7.3	12.5	Cerebellum
7	65	Lung	25	11.3	17.8	Frontal
8	81	Rectal	25	13.6	21.4	Cerebellum
9	77	Lung	30	7.9	13.3	Frontal
10	32	Breast	30	8.9	14.5	Insula

Table 1 : Patient characteristics

Table 2 : Results of the dosimetric parameters for the 10 patients according to the four treatment plans

	DCA	VMAT _{C_{Eclipse}}	VMATn _{C_{Eclipse}}	VMATn _{C_{Elements}}	Kruskal-Wallis Test p-value	Dunn Test p-value
Target Volume						
V70%	99.64 ± 0.12 (98.70 - 100.00)	99.26 ± 0.16 (98.90 - 100.00)	99.16 ± 0.13 (98.80 - 100.00)	99.00 ± 0.00 (99.00 - 99.00)	<i>ns</i>	
CI	1.28 ± 0.01 (1.23 - 1.31)	1.04 ± 0.01 (1 - 1.10)	1.05 ± 0.01 (1.01 - 1.10)	1.07 ± 0.01 (1.03 - 1.10)	< 0.001	DCA vs all VMAT Between all VMAT
GI	2.41 ± 0.05 (2.10 - 2.60)	3.02 ± 0.13 (2.50 - 3.50)	3.02 ± 0.13 (2.50 - 3.50)	2.45 ± 0.04 (2.20 - 2.70)	< 0.001	DCA vs VMATn _{C_{Eclipse}} VMATn _{C_{Eclipse}} VS VMATn _{C_{Elements}}
Healthy Brain						
V23.1Gy (cc)	9.35 ± 0.58 (7.10 - 12.30)	5.89 ± 0.56 (3.90 - 8.70)	5.58 ± 0.49 (3.60 - 8.30)	6.26 ± 0.36 (5.00 - 8.30)	< 0.001	DCA vs all VMAT Between all VMAT
V20Gy (cc)	12.81 ± 0.84 (9.40 - 17.40)	9.68 ± 0.93 (6.30 - 14.40)	8.62 ± 0.77 (5.60 - 13.10)	9.06 ± 0.58 (6.90 - 12.30)	< 0.01	DCA vs all VMAT Between all VMAT
V18 (cc)	15.52 ± 1.06 (11.10 - 21.60)	12.23 ± 1.18 (8.10 - 19.70)	10.94 ± 1.01 (7.10 - 16.90)	11.30 ± 0.75 (8.50 - 15.50)	< 0.05	DCA vs all VMAT Between all VMAT
Low-dose delivery						
V10Gy (cc)	40.14 ± 3.30 (26.20 - 58.30)	45.31 ± 5.49 (25.80 - 74.70)	30.09 ± 3.09 (19.30 - 50.00)	32.56 ± 2.61 (23.00 - 48.50)	<i>ns</i>	
V5Gy (cc)	109.71 ± 10.35 (69 - 155.40)	146.36 ± 19.43 (91.80 - 273.30)	82.01 ± 8.98 (47.90 - 133.00)	94.02 ± 8.18 (58.00 - 135)	< 0.05	VMATn_{C_{Eclipse}} VS VMAT _{C_{Eclipse}} VMATn_{C_{Elements}} VS VMAT _{C_{Eclipse}}

Data are presented as the mean doses of all patients ± standard deviation (min – max). Vx% (Gy) = minimum x% (Gy) of prescribed dose received by the volume. CI = Conformity index (Inverse Paddick). GI = Gradient index. VMAT = volumetric modulated arc therapy. DCA = dynamic conformal arcs (Iplan®). VMAT_{C_{Eclipse}} = VMAT technique with coplanar arcs only (Eclipse®). VMATn_{C_{Eclipse}} = VMAT technique with coplanar and non-coplanar arcs (Eclipse®). VMATn_{C_{Elements}} = VMAT technique with non-coplanar arcs (Elements Cranial SRS®). *ns* = non-significant. Techniques in bold means that the technique is superior for this organ in particular.