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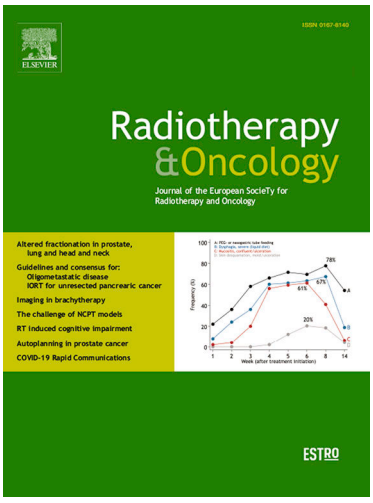

Original Article

Improving on whole-brain radiotherapy in patients with large brain metastases: A planning study to support the AROMA clinical trial

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Title

Improving on whole-brain radiotherapy in patients with large brain metastases: A planning study to support the AROMA clinical trial

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- Conflict of interest and funding statements

Conflict of interest

None.

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Clinical trial information

None.

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Data sharing statement

"Research data are stored in an institutional repository and will be shared upon request to the corresponding author."

Improving on whole-brain radiotherapy in patients with large brain metastases: A planning study to support the AROMA clinical trial

Abstract

Purpose:

To develop a novel dose-escalated volumetric modulated arc therapy (VMAT) strategy for patients with single or multiple large brain metastases which can deliver a higher dose to individual lesions for better local control (LC), and to compare dosimetry between whole brain radiotherapy (WBRT), hippocampal-sparing whole brain radiotherapy (HS-WBRT) and different VMAT-based focal radiotherapy approaches.

Methods and Materials:

We identified 20 patients with one to ten brain metastases and at least one lesion larger than 15 cm^3 who had received WBRT as part of routine care. For each patient, we designed and evaluated five radiotherapy treatment plans, including WBRT, HS-WBRT and three VMAT dosing models. A dose of 20 Gy in 5 fractions was prescribed to the whole brain or target volumes depending on the plan, with higher doses to smaller lesions and dose-escalated inner planning target volumes (DE-iPTV) in VMAT plans, respectively. Treatment plans were evaluated using the efficiency index, mean dose and D0.1cc to the target volumes and organs at risk.

Results:

Compared with WBRT, VMAT plans achieved a significantly more efficient dose distribution in brain lesions, especially with our DE-iPTV model, while minimising the dose to the normal brain and other organs at risks (OARs) ($p < 0.05$).

Conclusions:

VMAT plans obtained higher doses to brain metastases and minimised doses to OARs. Dose-escalated VMAT for larger lesions allows higher radiotherapy doses to be delivered to larger lesions while maintaining safe doses to OARs.

Keywords

Brain metastases; WBRT; VMAT; Dose-escalated planning; Local control

Abbreviations

Cumulative intracranial tumour volume (CITV)

Dose-escalated inner planning target volumes (DE-iPTV)

Disease-specific graded prognostic assessment (ds-GPA)

Dose-volume histograms (DVHs)

Gross tumour volume (GTV)

High-definition multileaf collimator (HD MLC)

Hazard Ratio (HR)

Half the prescription isodose (PIV 50%)

Hippocampal-sparing whole brain radiotherapy (HS-WBRT)

Local control (LC)

Organs at risks (OARs)

Overall survival (OS)

Planning target volume (PTV)

Stereotactic radiosurgery (SRS)

Target volume (TV)

Volumetric modulated arc therapy (VMAT)

Whole brain radiotherapy (WBRT)

Introduction

Metastatic brain tumours are the most common intracranial neoplasm. Exact incidence is unclear, but is estimated to occur in 8-20% of all cancer patients and is ten times more common than primary brain tumours [1, 2]. Overall survival (OS) of patients with brain metastases is poor, and although some patients with oligometastatic disease can live for years [3], 39% patients fail to receive any treatment and have a median survival of 42 days [4]. The main treatment options include surgery, stereotactic radiotherapy and whole brain radiotherapy, with the use of immunotherapy, chemotherapy or targeted agents in patients with treatment responsive tumour types.

Neurosurgery and stereotactic radiosurgery (SRS) are the most effective modalities for treatment but are only applicable to patients with limited smaller intracranial disease and adequate systemic disease control [5]. A recent survey of German radiation oncologists showed that for majority of patients with 4 - 10 brain metastases, WBRT was the most common treatment approach [6]. Unfortunately, outcomes in patients having WBRT are poor, with a median OS of 3 - 5 months, high rates of radiotherapy-induced neurocognitive deficits, and worse local control (LC) rates, especially for lesions of larger diameter [7, 8] and/or radioresistant histology. There is no absolute cut-off between “SRS treatable” and “large” metastases treated with WBRT, and different studies have used different criteria. Typically, studies describe large brain metastases as measuring either ≥ 2 - 4 cm in maximum diameter or ≥ 4 - 15 cm^3 in volume [9]. However, studies often fail to differentiate between the total volume of all lesions and the size of individual lesions. The disease-specific graded prognostic assessment (ds-GPA) offers the best prognostic performance, but does not explicitly include cumulative intracranial tumour volume (CITV), and predicts OS rather than response to treatment. Some studies have explored hypofractionated SRS in larger lesions [5, 7, 10-13] (e.g. 31 - 35 Gy in 5 fractions in metastases up to 91.5 cm^3 [12]; 5-fraction SRS for large tumours > 30 cm^3 with a median marginal dose of 31 Gy [13]). Nevertheless, most of these studies are retrospective and limited to patients with one to three brain metastases, and these approaches are not in routine practice, which tends to restrict the use of SRS in lesions > 3 cm in diameter or 10 cm^3 in volume [5, 11].

There have been multiple randomised trials assessing the impact of adding WBRT to focal therapy (surgery or SRS) for patients with limited brain metastases. Generally, they show that addition of WBRT reduces the risk of developing new lesions from about 50% to 25%, but does not improve OS. More recent work suggests that even in patients with > 5 metastases, SRS offers as good LC as WBRT, with less neuro-cognitive impact [14-16].

LC correlates with better symptom control, and its failure leads to worse quality of life [17]. Increasing intracranial metastatic volume is also directly related to both worse OS and LC. In a study by Nieder et al., 100% of lesions measuring > 10 cm^3 had local failure compared to only 48% in lesions < 0.5 cm^3 [18], consistent with other studies that show that local failure

rate is three times higher in lesions > 3 cm [7, 10, 19, 20]. In patients receiving SRS, LC rates increase with increasing dose. Abraham et al. observed that the volume receiving at least 32 Gy (V32; Hazard Ratio (HR), 0.069; $p < 0.0001$), or with higher prescription isodose (HR, 0.953; $p = 0.031$) were independent predictors of improved LC. One-year LC rate increased from 67% to 89% when V32 $\geqslant$ 24% ($p < 0.0001$) [19]. Vogelbaum et al. reported an increased risk of local failure for brain metastases treated with 15 Gy and 18 Gy compared to 24 Gy, with a one-year LC of 45%, 49% and 85%, while higher prescription dose exhibited significantly longer time to local failure ($p = 0.0005$) [21]. Furthermore, other studies also noticed that doses in excess of prescription dose were predictive of LC [22, 23].

Traditional WBRT is delivered using lateral parallel opposed fields. It has the advantage of low cost, basic equipment and training requirements and is quick to plan and deliver. In contrast, SRS requires specialised equipment and training, is not available in all centres and takes longer to plan and deliver. Volumetric modulated arc therapy (VMAT) is an approach to deliver complex radiotherapy doses and is now widely available in radiotherapy departments worldwide. Compared to traditional brain radiotherapy approaches, VMAT offers the potential to deliver better target conformity and reduced doses to normal structures, with only slightly increased treatment times. In the meanwhile, for patients with large metastases, VMAT may offer as good dosimetry as stereotactic approaches, with better dose conformity to the target and lower doses to the organs at risks (OARs) than WBRT [11], and much shorter treatment time than for SRS [24, 25]. For patients with significant symptoms and a short life-expectancy, it is reasonable to ask if the additional time taken to plan and deliver SRS is acceptable to patients.

In patients who are not suitable for surgery or SRS, WBRT delivers too little dose to the target lesions (thus reducing response and local control) and too much dose to normal brain (increases side effects). The beneficial effect of WBRT on reducing new lesions is less important, given the very poor prognosis in this group. SRS is unlikely to be feasible in this population, but we might be able to use VMAT to increase the dose to lesions while reducing the dose to normal brain, and in particular to use VMAT to increase the dose to larger lesions. We have therefore started planning the AROMA trial to assess the potential benefits of delivering higher radiotherapy doses, delivered using VMAT, to patients with multiple brain metastases who are not suitable for SRS and would otherwise be offered WBRT. The intention is to conduct a pragmatic randomised trial of the two different radiotherapy approaches, with a focus on patient quality of life as the primary outcome measures.

In order to assess the feasibility of our approach for a potential clinical trial, we conducted a planning study to assess the dosimetric outcomes of our novel dose escalation model for VMAT in patients with large brain metastases in the context of five radiation regimens. This included WBRT, hippocampal-sparing WBRT (HS-WBRT) and three VMAT dosing models. Assessing the quality of radiotherapy dosimetry is problematic, especially in patients with multiple lesions. Commonly used SRS metrics, such as conformity index, homogeneity index and gradient index are not definable for multiple metastases with different dose prescriptions in combination with whole brain radiotherapy, and so we have used the efficiency index, as well as doses to lesions and OARs to measure the quality of radiotherapy [26].

Methods

We identified all patients with brain metastases treated with WBRT in Charing Cross Hospital, Imperial College Healthcare NHS Trust, London, between April 2017 and December 2019. Since this was a retrospective review of patient data and replanning, we did not require formal research approvals. However, it was registered as part of the over-arching neuro-oncology Quality Improvement programme within the department. We manually reviewed imaging and identified those adult patients who had a pre-treatment T1-contrast MRI sequence, had ten or fewer brain metastases and at least one metastasis ≥ 15 cm^3 in volume or ≥ 3.5 cm in longest diameter. We excluded patients who had had previous treatment to the lesion (i.e. surgery, SRS, WBRT), or patients with leptomeningeal disease. Patients who had lesions within 5 mm of hippocampi bilaterally were excluded due to ineligibility for HS-WBRT. We evaluated a series of increasingly complex plans and dosing regimens, but kept all radiotherapy schedules to 5 fractions in order to ease comparison and ensure similarity between study arms.

The planning CT scans for the previous WBRT were used in our planning study, which were in 3mm slice thickness (Philips Brilliance Big Bore CT, Philips, Cleveland OH) with patients immobilized in head first and spine position using Vertec Thermoplastic shells (Vertec, Reading, UK). We fused MRI and planning CT scans and outlined all visible lesions on the volumetric T1-contrast MRI scans as gross tumour volume (GTV). Planning target volume (PTV) was then developed by an isotropic 1 mm margin from GTV. OARs included the normal brain, eyes, lenses, chiasm, optic nerves, brainstem, cochlea and hippocampi, and they were outlined for dose constraints and evaluation. Hippocampi were outlined according to RTOG 0933 contouring atlas [27]. Normal brain volumes were defined as whole brain volume with the subtraction of the GTV. Dose constraints followed the general constraints presented in Supplement table 1 [28-30], and in particular, we constrained V24.4 to be less than 10 cm^3 of normal brain to limit the predicted risk of radionecrosis to ≤ 5% for five-fraction radiation [31]. We considered dose constraints on all OARs prior to the dose on PTVs. All plans were carried out based on the same GTV, PTV and OAR contouring for comparison. All plans were generated using Varian Truebeam 6MV with a high-definition multileaf collimator (HD MLC) in the Eclipse planning system using standard clinic settings, 2.5mm dose grid and 2 degree control point spacing (Version 15.6, Varian Medical Systems Inc., Palo Alto, CA, USA). No manual adjustments of optimisation were applied. All outlining and planning was conducted by an experienced radiation-oncology fellow (JC) with outlining reviewed by an experienced neuro-oncology consultant (MW) and planning reviewed by an experienced radiation physicist (LH).

WBRT

For WBRT plans, we used the original plan that patients received, using conventional opposed lateral fields. The dose was prescribed to 20 Gy in 5 fractions for all WBRT plans (Figure 1 A).

HS-WBRT

All HS-WBRT plans were planned using VMAT based on a mono-isocentric technique with two coplanar 360°-arcs of Truebeam Linac 6MV flattened beam. Hippocampal avoidance regions were developed with a geometrical isotropic expansion of 5 mm to the hippocampus [29, 30] unless there was a lesion within 5 mm of a hippocampus, in which case we only spared the contralateral hippocampus. We prescribed 20 Gy in 5 fractions to the whole brain with 3 mm expansion, sparing the hippocampal avoidance regions (Figure 1 B).

VMAT

We developed three different 5-fraction VMAT dosing models for all patients. All the models had to meet the requirement that 98% of the target volumes were irradiated with at least 20 Gy as mandatory without an upper dose limit within the target volumes. We followed a combination of guidance from the UK Consensus guidance for stereotactic radiotherapy, HyTEC reports, AAPM report and the HIPPO phase 2 RCT protocol to set dose constraints on the OARs [28, 30-32]; where an OAR had differing dose constraints in two sets of guidance, we took the more conservative (lower) dose limit. All VMAT plans used a mono-isocenter technique with two coplanar 360°-arcs.

In the first model ("VMAT20all"), all target volumes were prescribed 20 Gy to allow easy comparison with the WBRT and HS-WBRT plans (Figure 1 C). In the second model ("VMAT20/25"), we increased the prescribed dose to 25 Gy for small lesions (< 15 cm^3), while maintaining the dose at 20 Gy for large lesions (≥ 15 cm^3) (Figure 1 D). In the third model ("VMAT20/25boost"), DE-iPTV were developed by isotropically shrinking the PTV volume in 5 mm steps. Small lesions were again prescribed 25 Gy, while larger lesions received 20 Gy to the initial PTV, while each DE-iPTV received a 10 Gy stepwise increase per step (Figure 1 E). Thus, larger lesions received progressively higher doses to the central portions of the lesions.

Plan evaluation

To evaluate the quality of the plans, dose-volume histograms (DVHs) for the whole brain and key OARs were reviewed along with data for each lesion irradiated. Since we expected most

patients to have > 1 lesion, and the Gradient Index does not accurately describe multi-target plans, in line with previous work we used Integral Dose and the Efficiency Index for plan evaluation [26]. The Integral Dose simply sums the different dose levels across a target volume and provides a measure of how much dose is deposited in the target overall, while the Efficiency Index is the ratio of target Integral Dose to the Integral Dose for the volume defined by the 50% prescription isodose, and so measures how relatively effective the plan is at delivering dose to the target without delivering dose to normal tissue.

Integral dose for a target volume (TV) was defined in the equation as follows:

$$Integral\ Dose_{TV} = \int_{Dmin}^{Dmax} TV\delta dose = Mean\ Dose_{TV} \times Volume_{TV}$$

When evaluating the integral dose on metastases, the integral dose of every lesion was summed up as Integral $Dose_{MET}$ and divided by total target volumes for the weighted average mean dose.

$$Integral\ Dose_{MET} = Integral\ Dose_{MET1} + Integral\ Dose_{MET2} + \ldots + Integral\ Dose_{METn}$$

$$Mean\ Dose_{MET} = \frac{Integral\ Dose_{MET}}{Total\ target\ volumes}$$

The efficiency index was calculated as the ratio of the integral dose of metastases to the integral dose of the global volume of half the prescription isodose (PIV 50%). We considered 10 Gy as half the prescription isodose since we prescribed 20 Gy to the whole brain and large lesions in our study.

$$Efficiency\ Index = \frac{Integral\ Dose_{MET}}{Global\ Integral\ Dose_{PIV50\%}}$$

We also compared D0.1cc on OARs and V24.4 on the normal brain to analyze the impacts in terms of normal tissues sparing of different regimens.

The design and the quality of the study were accessed according to the RATING guideline [33].

Data analyses

Statistical analysis was performed using GraphPad 9 software (GraphPad Software, Inc, USA). The normal distribution of data was examined with the Shapiro-Wilk test. One-way repeated measures ANOVA or paired t-test was used to compare differences between groups when all data groups passed normality test, otherwise, Friedman test or Wilcoxon matched-pairs signed-rank test was applied. We defined two-tailed $p < 0.05$ as statistical significance.

Results

We identified 142 patients treated with WBRT of whom, 21 had at least one brain metastasis ≥ 15 cm^3 in volume. One patient was excluded due to lesions within 5 mm of hippocampi bilaterally. Therefore, 20 patients met the criteria and were included for further evaluation (Table 1, Supplement figure 1). There were 60 lesions in total with a mean volume of 11.4 cm^3 (range 0.1 - 60.9 cm^3, median 1.9 cm^3, IQR 0.4 - 23.0 cm^3). Seven patients had a single large lesion, one patient had two lesions larger than 15 cm^3. Four patients had a brain metastasis within 5 mm of one hippocampus, so we only considered unilateral HS-WBRT plans.

Compared with WBRT and HS-WBRT, all VMAT models significantly increased the efficiency index from 0.021 to over 0.226 (Figure 2, Supplement table 2; $p < 0.0001$). These differences were true across all patients (Figure 3 A), patients with multiple lesions (Figure 3 B) and those with a single lesion (Figure 3 C). All three VMAT models exhibited comparable efficiency with no significant difference (Supplement figure 2 A-C).

As illustrated in Supplement table 2 and Figure 3 D-E, all three VMAT models achieved higher mean dose and D0.1cc on brain metastases ($p < 0.05$). To determine the impact of lesion volumes, we stratified the analyses into large (≥ 15 cm^3) and small (< 15 cm^3) lesions (Figure 3 F-I). Similar results were obtained in both groups, suggesting that dosimetry was improved irrespective of lesion size compared to WBRT ($p < 0.05$). Dose on target volume were significantly higher when planned with the "VMAT20/25boost" model regardless of single lesion or multiple lesions ($p < 0.05$) (Figure 3 J-M). Comparing the three VMAT models, the "VMAT20/25boost" model still significantly increased the irradiation dose in brain metastases above the two other VMAT models ($p < 0.05$) (Supplement figure 2 D-M).

Taken together, this suggests that moderately dose-escalated VMAT could deliver significantly higher doses, even into small metastases, and larger metastases can be further dose-escalated while maintaining agreed normal-brain safe dose limits.

VMAT plans delivered less dose than either WBRT or HS-WBRT to the normal brain ($p < 0.0001$) (Supplement table 3, Figure 4 A). Even dose-escalated VMAT plans ("VMAT20/25" and "VMAT20/25Boost") did not significantly increase the normal brain dose. Importantly, V24.4 was controlled within an acceptable level even when an escalated dose was prescribed with VMAT plans. V24.4 remained ≤ 10 cm^3 except in three plans (one plan with VMAT20/25 and two plans with VMAT20/25boost) on two patients with eight and nine metastases, when we had to reduce the prescription dose to meet the constraints. It is worth noting that the V24.4 was 0 cm^3 with both WBRT and HS-WBRT, where the maximum prescribed dose was 20 Gy (Figure 4 B). Similar findings were seen for doses to specific OARs (Figure 4 C-P). In particular, the three VMAT planning approaches all achieved lower hippocampal doses than HS-WBRT. Accordingly, these findings indicated better OARs sparing with all VMAT plans even with the "VMAT20/25boost" model.

The RATING score for our study was 95% and the RATING fraction was 200 of 210 (Supplement table 4).

Discussion

In this study, we compared five different radiotherapy planning approaches in 20 patients who had multiple brain metastases and at least one large lesion (≥ 15 cm^3), who had received WBRT in routine clinical practice. Our results illustrated the superior dosimetric distribution of VMAT when treating large brain metastases. Furthermore, our novel DE-iPTV VMAT approach could successfully deliver significantly higher doses onto the brain metastases for both larger and smaller metastases with better OARs sparing compared with WBRT.

Consistent evidence has indicated that the increasing volume of brain metastases is directly related to inferior OS and LC [10, 19, 21]. However, due to the lack of sufficient data from randomized clinical trials and concerns about the safety of SRS in patients with large lesions, WBRT remains the standard treatment regimen for large multiple brain metastases. Unfortunately, the outcomes of WBRT are disappointing. Our patients were drawn from a tertiary neuro-oncology centre, with integrated neurosurgery and neuro-oncology service, including access to SRS. Those patients included in this study were those that, despite access to services, were treated with WBRT by their primary consultants.

LC is improved with increases in dose delivered to lesions [19, 21]. Our replanning study showed an increase in the dose delivered to lesions. Both integral dose and D0.1cc on target volume significantly increased with VMAT plans irrespective of lesion size and this was more pronounced with the “VMAT20/25boost” inner-escalated dosing model when compared with other VMAT plans. Accordingly, these results demonstrated that our inner-escalated dosing VMAT model is superior in delivering higher dose to the brain metastases and thus likely achieves better LC. Notably, the OARs received a significantly lower dose in all VMAT plans, including the inner-escalated dosing model, indicating better sparing of normal tissue with VMAT as compared to WBRT, which should reduce the chance of radiation-induced toxicity.

The major concern of prescribing a higher dose is the increased risk of radionecrosis. Data from fractionated SRS using a 5-fraction regimen suggests expected toxicity rates of 4.8% for V24.4 of 10 cm^3 and 8.6% for V24.4 of 20 cm^3 of normal brain [13, 31, 34]. While the escalated dosing models lead to higher V24.4 in the normal brain than WBRT, we were able to keep V24.4 ≤ 10 cm^3. The mean V24.4 range was 1.11 - 4.30 cm^3 across all VMAT plans. Therefore, even with our escalated dose approach, the risk of radionecrosis remains reasonably low though there may be a higher risk for patients with more than eight lesions. Once we consider the poor prognosis of these patients, the actual risk of radionecrosis is likely to be very low. We are planning further work to integrate prognostic models with dosimetry to allow for an explicit time-based trade-off between toxicity and dosimetry.

Our study has some limitations. Only 20 patients with large brain metastases were included in this study and proportion of patients with more than five lesions was small. Additionally, all five models were prescribed with 20 Gy in five fractions in line with WBRT. The safety and dosimetry with higher prescription dose using the VMAT plan, especially our DE-iPTV

approach, is yet to be identified in our further planning studies supporting the AROMA clinical trial.

Conclusion

For patients with large brain metastases, VMAT-based radiotherapy plans, in particular our DE-iPTV approach, achieved more efficient dose distribution targeting of brain lesions while reducing the dose to the normal brain and other OARs compared with WBRT. Therefore, VMAT is a promising approach for patients with multiple large brain metastases. Importantly, it is much more widely available and quicker to plan and deliver than SRS. Therefore, in this large group of patients, VMAT may be potentially a better solution for multiple large brain metastases treatment.

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Author contribution

All authors made a substantial contribution to the design of the paper, the interpretation of the results, and the final version of the paper. J Chen and M Williams wrote the paper, with the support and input of the other authors. J Chen, M Williams and L Hill carried out the radiation planning. J Chen also produced the data and the graphs, and provided the data for the tables. J Chen and M Williams provided the statistical analysis. All authors provided references used in the paper. I confirm that I had full access to all data in the study and had final responsibility for the decision to submit for publication (J Chen).

Conflict of interest

None.

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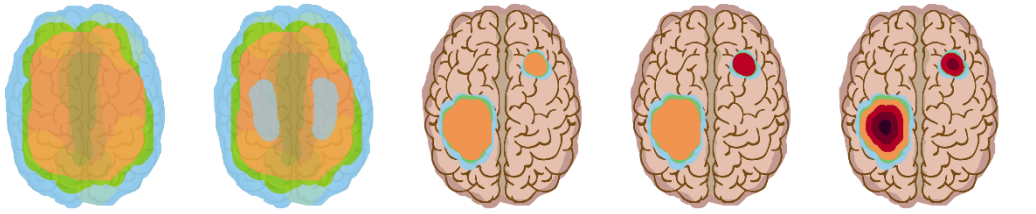
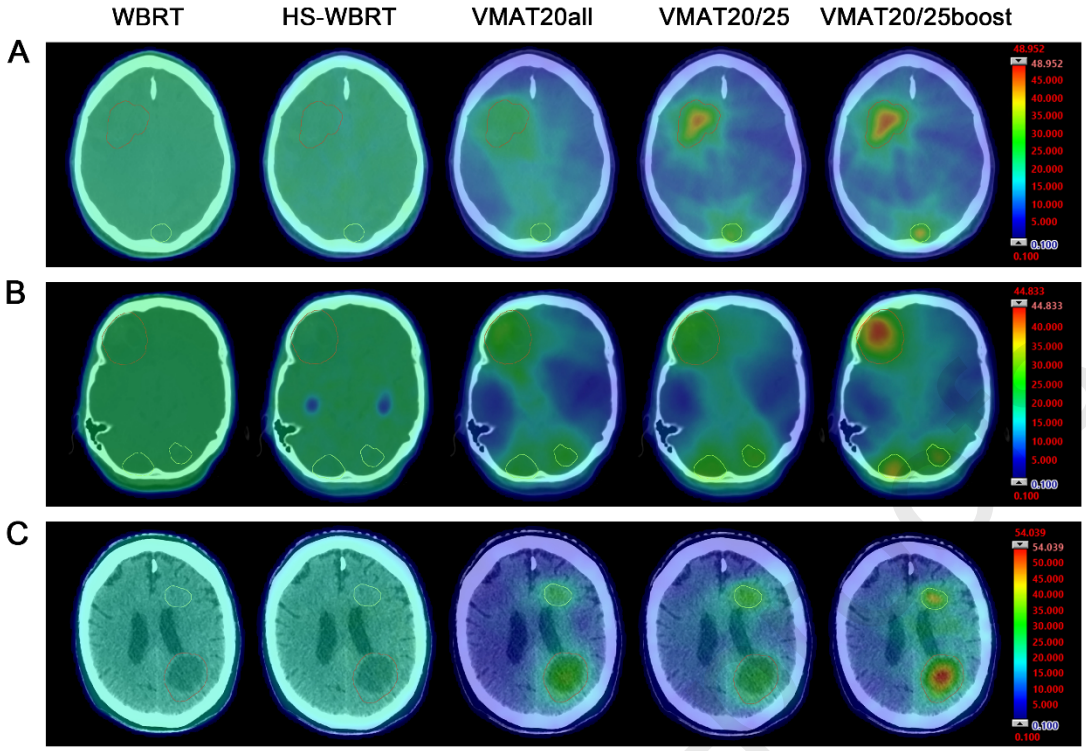
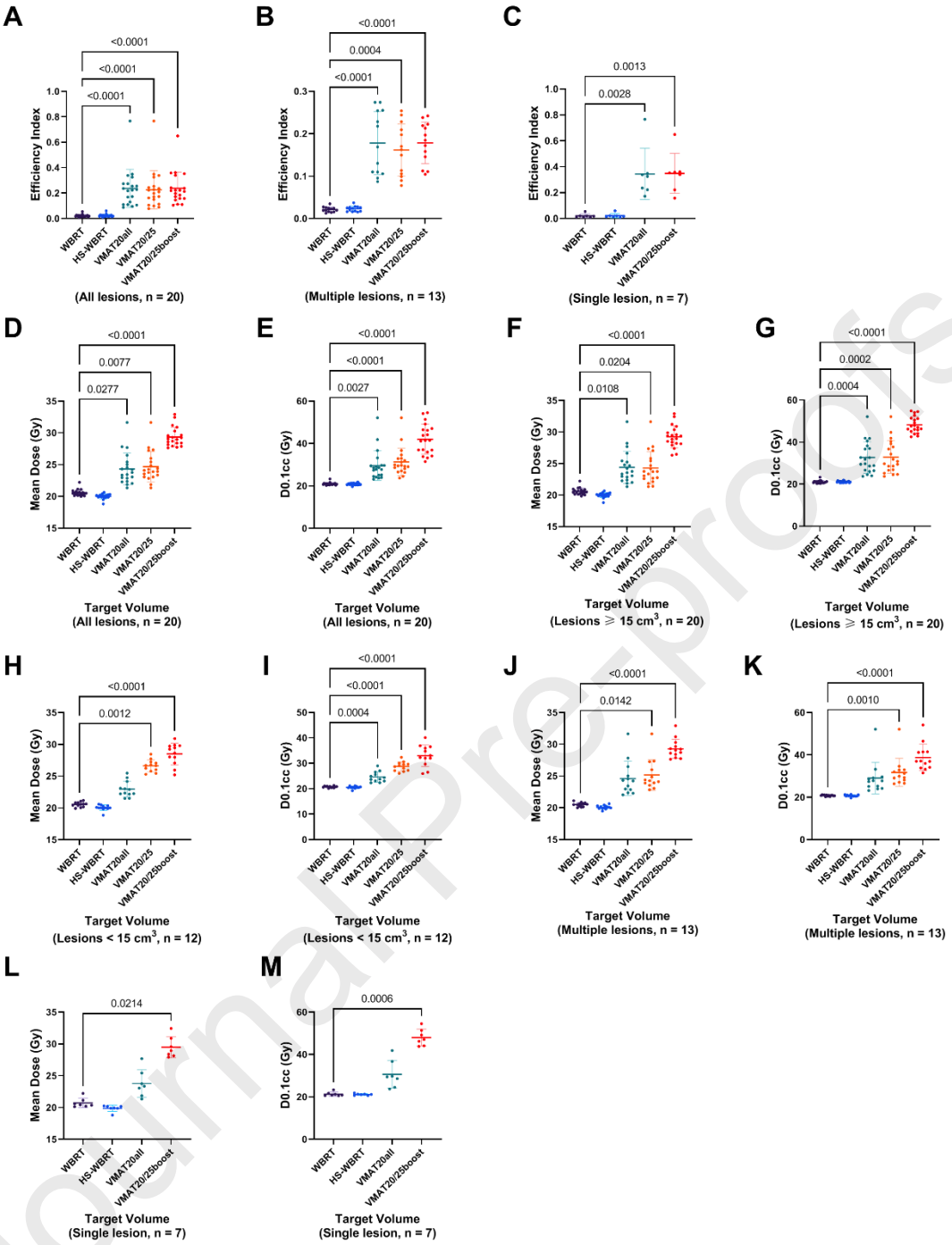






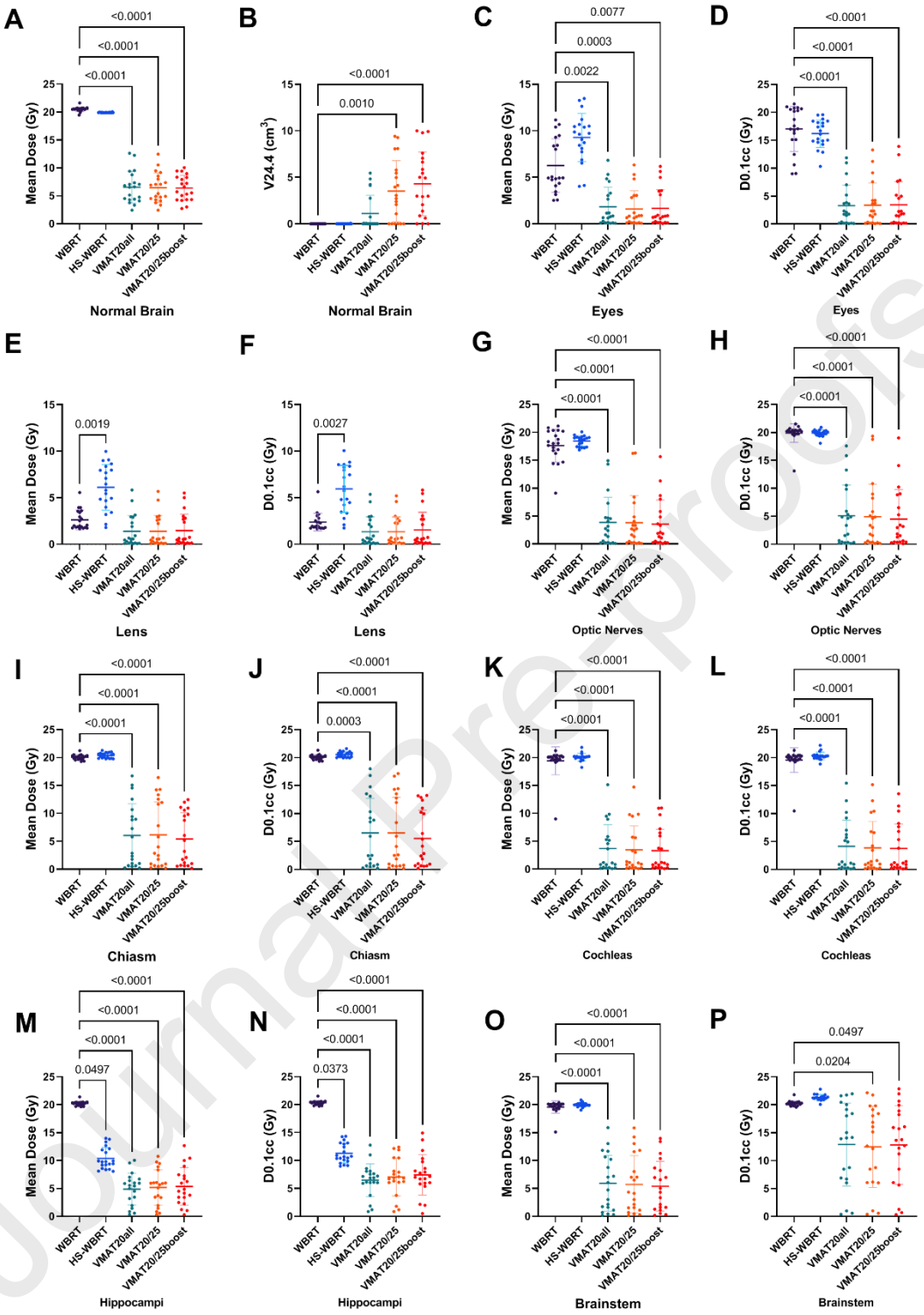


Figure 1. Different 5-fraction radiation models on brain metastases. **(A)** Conventional opposed lateral whole brain radiation (WBRT) with 20 Gy in 5 fractions. **(B)** Hippocampal-sparing WBRT (HS-WBRT) with 20 Gy in 5 fractions. **(C)** Volumetric modulated arc therapy (VMAT) with 20 Gy in 5 fractions on all brain metastases ("VMAT20all"). **(D)** VMAT with 20 Gy on lesions ≥ 15 cm^3 and 25 Gy for lesions < 15 cm^3 in 5 fractions ("VMAT20/25"). **(E)** Inner PTVs were developed by shrinking the PTV at every 5 mm from the outer surface. PTVs are

prescribed with 20 Gy and 25 Gy in 5 fractions based on the size of lesions as described in "VMAT20/25", while a dose escalation of 10 Gy as the optimal escalated dose for every inner PTV available ("VMAT20/25boost").

Figure 2. Example of dosimetry. **(A)** Patient No. 14. **(B)** Patient No. 16. **(C)** Patient No. 17. Line in red = planning target volume (PTV) for lesions ≥ 15 cm^3; line in yellow = PTV for lesions < 15 cm^3.

Figure 3. Efficiency index and dosimetric characteristics on brain metastases. Bar plot represented mean ± SD. The *p* values were presented where $p < 0.05$ compared with WBRT.

Figure 4. Dosimetric characteristics on OARs. Bar plot represented mean ± SD (n = 20). The *p* values were presented where $p < 0.05$ compared with WBRT.

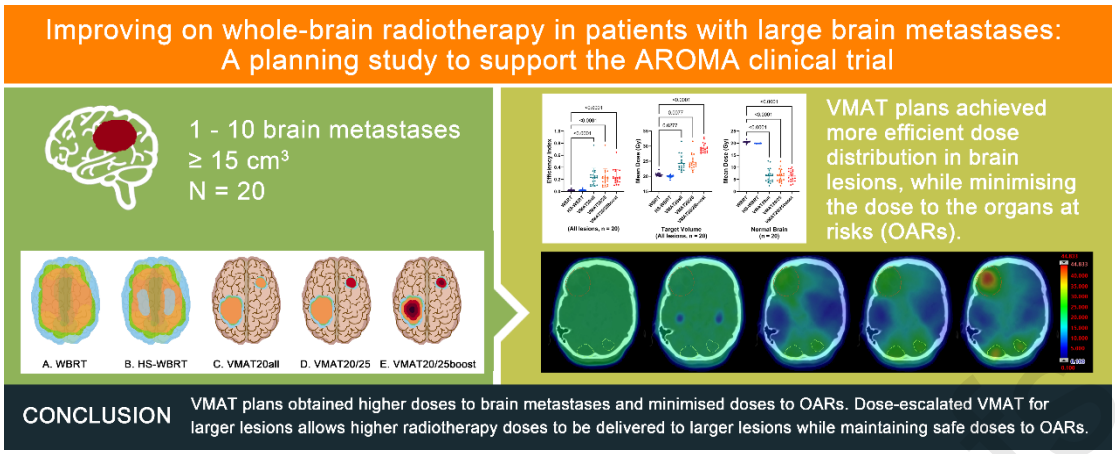
Table 1. Patients and metastases characteristics.

Patient No.	Gender	Age at the time of treatment	Primary Tumour	Number of Brain Metastases	Number of Large Metastases (⩾ 15 cm^3)	Volume of the Largest Metastases (cm^3)	Total Volume of Brain Metastases (cm^3)
1	Male	66	Oesophagus	1	1	37.9	37.9
2	Female	60	Breast	1	1	16	16
3[&]	Female	79	Breast	2	1	18.8	20.6
4	Male	69	NSCLC	1	1	60.9	60.9
5[#]	Female	71	Oesophagus	5	1	34	37
6	Female	61	Oesophagus	2	1	23.3	25

7[#]	Male	50	NSCLC	1	1	25.5	25.5
8	Female	76	Rectum	2	1	25.1	25.6
9[#&]	Female	72	Ovary	1	1	33.1	33.1
10	Female	68	NSCLC	1	1	32.1	32.1
11	Female	61	Breast	1	1	20.9	20.9
12	Male	69	NSCLC	2	2	23.2	43.4
13	Male	62	Colon	4	1	23.7	24
14	Male	66	NSCLC	5	1	39.7	46.8
15	Female	88	Myeloma	4	1	32.1	35
16	Female	55	Sigmoid	8	1	31.5	48.8
17	Male	66	SCLC	2	1	34.6	38.7
18[#]	Male	65	NSCLC	3	1	41.6	46.7
19	Female	60	Breast	9	1	18.5	29.8
20	Male	71	SCLC	5	1	22.3	34.5

Lesion within 5mm of unilateral hippocampi.

& Lesion with brainstem invasion.



Radiotherapy for 1 to 10 brain metastases and at least one lesion larger than 15 cm^3

Comparison of VMAT plans with WBRT and HS-WBRT

Development of a novel dose-escalated internal PTV model with VMAT

Performance of dose distributions within the tumours and OARs

Conflict of interest and funding statements

Conflict of interest

None.

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Clinical trial information

None.

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