Original Article

Multiple Brain Metastases Radiosurgery with CyberKnife Device: Dosimetric Comparison between Fixed/Iris and Multileaf Collimator Plans

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Abstract

Purpose: In our institution, stereotactic radiosurgery of multiple brain metastases is performed with the CyberKnife® (CK) device, using fixed/Iris collimators. In this study, nineteen fixed/Iris plans were recalculated with the multileaf collimator (MLC), to assess if it is possible to produce plans with comparable dosimetric overall quality. **Materials and Methods:** For consistent comparisons, MLC plans were re-optimized and re-normalized in order to achieve the same minimum dose for the total planning target volume (PTV_{tot}). Conformation number (CN), homogeneity index (HI) and dose gradient index (DGI) metrics were evaluated. The dose to the brain was evaluated as the volume receiving 12 Gy (V_{12}) and as the integral dose (ID). The normal tissue complication probability (NTCP) for brain radionecrosis was calculated as a function of V_{12}. **Results:** The reoptimized plans were reviewed by the radiation oncologist and were found clinically acceptable according to the The American Association of Physicists in Medicine (AAPM) Task Group-101 protocol. However, fixed/Iris plans provided significantly higher CN (+8.6%), HI (+2.2%), and DGI (+44.0%) values, and significantly lower ID values (−35.9%). For PTV_{tot} less than the median value of 2.58cc, fixed/Iris plans provided significantly lower NTCP values. On the other side, MLC plans provided significantly lower treatment times (−18.4%), number of monitor units (−33.3%), beams (−46.0%) and nodes (−21.3%). **Conclusions:** CK-MLC plans for the stereotactic treatment of brain multi metastases could provide an important advantage in terms of treatment duration. However, to contain the increased risk for brain radionecrosis, it could be useful to calculate MLC plans only for patients with large PTV_{tot}.

Keywords: Brain radiosurgery, CyberKnife®, dosimetric comparison

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Introduction

Brain metastases develop in 20%–40% of patients diagnosed with solid tumors.[1] Thanks to the development in systemic treatment, the number of patients living with brain metastasis has increased. For a long time, whole brain radiotherapy has been considered the standard treatment for patients with brain metastases, but it is associated with cognitive decline. In contrast, stereotactic radiosurgery (SRS) has proved to have an excellent local control, preserving cognitive function and quality of life. Therefore, SRS has become the standard of care for patients with 1–3 metastases,[2-4] and many centers explored its use in patients with more than 3 metastases. A prospective observational trial has demonstrated no decrease in survival or increase in local recurrence or toxicity in patients treated for 2–4 versus 5–10 brain metastasis.[5]

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However, in SRS treatments radionecrosis, edema, and other neurologic complications are common.[6] The incidence of radionecrosis depends on the dose, volume, region irradiated and other parameters, including conformity index and overall treatment times.[7]

SRS treatments can be performed with standard linear accelerators or dedicated stereotactic machines such as Gamma Knife or CyberKnife. The CyberKnife (CK) (Accuray Incorporated, Sunnyvale, USA) is a robotic image-guided

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device, specifically developed for intra-and extra-cranial radiosurgery treatments. Through the use of nonisocentric noncoplanar beams of various size, the system can deliver highly inhomogeneous dose distributions with very steep gradients.[8] The system provides different secondary collimator options: 12 fixed cone collimators, an Iris collimator with a 12-sided computer controlled adjustable aperture, and a multileaf collimator (MLC).

In our institution, small spherical-shaped targets are usually treated with fixed cone or Iris collimators, which minimizes transmitted doses and thus maximally spares the surrounding normal tissues. However, fixed/Iris plans typically require a higher number of monitor units (MUs) and longer treatment times, depending on plan complexity and number of lesions. For brain multiple metastases SRS, the treatment time of a fixed/Iris collimator plan could range from about 30 to more than 60 min. This could be a critical limitation since patients are often painful and not compliant. On the contrary MLC plans commonly require shorter treatment times and would ease the treatment of such patients. A streamlining of the workload could also be favorable in view of the fact that CK machines are becoming more widely distributed and the range of eligible treatment targets is broadening which results in potentially longer patient lists. On the other hand, extending the use of the MLC collimator may have relevant clinical implications. Indeed, at our institution, MLC collimator is employed for the treatment of irregularly shaped targets usually much larger than typical brain metastases, such as brain meningioma, spine metastases, or prostate cancers. When treating small targets, MLC could lead to a higher integral dose (ID) to the surrounding tissues due to MLC leaves transmission. Moreover, the wider margin of MLC leaves around the targets compared to fixed\Iris collimators could give an additional dose contribution to normal tissues.

In this study, we retrospectively recalculated nineteen fixed/Iris clinical plans with the MLC collimator for patients affected with multiple brain metastases, to assess if it is possible to produce plans with comparable overall quality in terms of target coverage, dose conformity/homogeneity, dose gradient, and with an acceptable dose to normal tissues surrounding the lesion.

Materials and Methods

CyberKnife device

CyberKnife–M6 is a robotic system designed for stereotactic treatments.[9-11] A linear accelerator is mounted on an industrial robot with a 6-axis manipulator arm, producing 6 MV flattening filter free (FFF) photons at a fixed dose rate of 1000 MU/min. The device allows the delivery of several nonisocentric noncoplanar beams and tracks the target position with two orthogonal imaging systems, ensuring sub-millimeter accuracy.

CyberKnife–M6 is provided with three collimator types: (i) Twelve fixed collimators, with circular apertures ranging from 5 mm to 60 mm diameter, defined at a source-to-axis distance (SAD) of 800 mm; (ii) an Iris collimator, composed of 2 hexagonal banks of tungsten segments that produce dodecagonal apertures with the same sizes of fixed collimators; (iii) an InCise™ MLC, with 2 banks of 41 tungsten leaves 2.5 mm wide and 90 mm thick with full interdigitation and overtravel, to create shapes as small as 7.6 mm × 7.5 mm, and as large as 100.0 mm × 97.5 mm at 800 mm SAD.

Patients selection, target definition, and dose prescription

Nineteen patients with at least three brain metastases were selected for the study. All patients were treated at our institution between October 2019 and May 2021 with the CyberKnife device. All clinical plans were calculated using fixed cones or Iris collimator.

Computed tomography (CT) images of 1.25 mm slice thickness produced by a GE Lightspeed CT scanner (GE Healthcare, Boston, USA) were used as primary planning images. Magnetic resonance images (0.5 mm slice thickness) were co-registered with CT images for delineating target volumes.

Radiation oncologists used Eclipse treatment planning system (TPS) (Varian Medical Systems, Inc., Palo Alto, USA) version 15.6 to contour gross tumor volumes (GTVs) and organs at risk (OARs), following standard contouring protocols. Planning target volumes (PTVs) were obtained giving a 1.5 mm margin to GTVs. A total PTV (PTV_{tot}) given by the sum of all PTVs was considered. For serial OARs a planning organ at risk volume was obtained giving a 1.5 mm margin.

At present, there is no specific guideline for the minimum or maximum dose prescribed to the target in SRS planning.[12] At our institution, 18–21 Gy in 1–3 fractions, depending on lesion volumes, are prescribed. The dose was normalized so that the 100% isodose line encompassed more than 98% minimum dose to any lesion included in PTV_{tot}. On average, the typical isodose line that corresponded to this coverage was 87%, in agreement with other works in the literature.[13-15] All the patients in this study were treated with 21 Gy in a single fraction.

Treatment planning

All plans were calculated with the Precision TPS (Accuray Incorporated, Sunnyvale, USA), version 2.0.1.1. Clinical and recalculated plans were setup with "head_Iris-Fixed" and "head_MLC" treatment anatomy, respectively, "full_path" as template path set and "6D skull" as the tracking method. Beam's direction was always set to never intersect with the eyes. The optimization was performed using the VOLO™ optimizer.[16,17] In VOLO™, available optimization goals are maximum dose, minimum dose and dose-volume objectives for both targets and OARs. No hard constraints are available. For each structure, up to five objectives could be assigned with different priorities. On average, three shells were created to control the dose fall-off around the targets. The shells were obtained giving a 1.5 mm, a 10 mm, and a 20 mm isotropic margin around PTV_{tot}, and were assigned with a maximum dose of 100%, 50%, and 30% of prescription dose (PD), respectively.

The maximum number of nodes is variable according to the target position and the path of the machine. We decided to give the maximum freedom of movement to the robotic arm, always setting the maximum number of nodes to the highest available value.

Optimization parameters include the maximum number of nodes, the maximum number of optimization iterations (range 50–500), the total MU penalty (range 0–10), the minimum number of MUs per beam (or segment) per fraction (range 2–100), the maximum number of MUs per beam (or segment) (range 100–5000), and the maximum total number of beams (or segments) (range 20–500).

The total MU penalty is a specific optimization parameter useful to reduce the delivery time. The algorithm estimates the delivery time, summing the time required for the patient setup, the time spent by the robot to move between nodes, the time required for imaging, and the beam-on time.

The minimum number of MUs set the MU threshold per beam (or segment) per fraction.

The minimum number of MUs per beam (or segment) was set at least at 4 MUs per fraction, to ensure our linac linearity. All other optimization parameters were set to default or intermediate values, since in the selected patients the lesions were far from serial OARs, and no extreme dose gradient was required.

In order to provide a consistent comparison, in each MLC plan the optimization engine was run with the same values of optimization goals and parameters that were used for the corresponding clinical plan.

For MLC plans, optimization parameters included the fluence smoothness penalty (range 0–10), the number of adaptation iterations (range 0–5), and the maximum MUs per beamlet (range 120–6000). These three parameters were set to the default values. The fluence smoothness penalty is useful to make neighboring beamlets more homogeneous. The number of adaptation iterations influences the MLC leaf positions and consequently the MLC aperture size.[17]

The final dose calculation was performed with the ray tracing algorithm and contour correction for fixed/iris plans and with the finite size pencil beam algorithm and lateral scaling for MLC plans, using the high dose grid resolution. Although Monte Carlo algorithm is also available, it was not used because no lesion was in proximity to air cavities. After dose calculation, MLC plans were re-normalized in order to achieve for PTV_{tot} the same minimum dose (D_{min}) as that obtained for the corresponding clinical plans. The recalculated plans were found clinically acceptable by the radiation oncologist based on the dose constraints suggested by the AAPM Task Group (TG)-101 for SRS treatments.[18]

Plan quality assurance

Planning accuracy of both fixed/Iris and MLC plans was validated using SRS MapCHECK and StereoPHAN (Sun Nuclear Corp, Melbourne, USA) system. SRS MapCHECK is a 1013 n-type diode matrix that covers an active area of 77 mm × 77 mm. The diodes have a submillimetric resolution (0.48 mm × 0.48 mm area and 0.007 mm^3 volume) and high sensitivity, around 15 nC/Gy.[19,20] StereoPHAN is a polymethyl methacrylate (PMMA) head-shaped phantom designed to accommodate SRS MapCHECK. The detector interfaces with the SNC software version 8.3 (Sun Nuclear Corp., Melbourne, USA).

For both fixed/Iris and MLC plans, a quality assurance (QA) plan was calculated, measured, and compared with the dose calculated at the TPS using a local-pixel-dose-difference of 2%, a distance-to-agreement of 2 mm and a lower threshold for the gamma pass-rate of 90%, as suggested by the AAPM TG-135[21] for stereotactic treatments.

Dosimetric comparison

In order to evaluate the differences between fixed/Iris clinical plans and MLC recalculated plans, we considered conformity, homogeneity, and gradient metrics. The conformation number (CN) is defined by equation 1.[22]

$$CN = \frac{TV_{RI}^{\ 2}}{TV_{tot} . V_{RI}} \quad (1)$$

TV_{RI} (cc) is the target volume receiving the PD, TV_{tot} (cc) is the total target volume and V_{RI} (cc) is the body volume receiving the PD. CN is ≤1, the latter case being the ideal one.

The homogeneity index (HI) is defined by equation 2[23] as the ratio between the maximum point dose in the plan (D_{max}) and the PD.

$$HI = \frac{D_{max}}{PD} \quad (2)$$

In SRS treatments a high D_{max} within the target is desired because it may improve local control and any recurrence.[24] Moreover, freedom in the dose upper limit potentially allows distributions with steeper gradients at the PTV-normal tissue interface.

The dose gradient index (DGI) is described by equation 3.[14,25]

$$DGI = 100 - \left\{100.\left[\left(R_{eff,50\%PD} - R_{eff,PD}\right) - 0.3\right]\right\} \quad (3)$$

Here, $R_{eff,PD} = \sqrt[3]{3V / 4\pi}$ (cm) is the effective radius (i.e., the radius of a sphere of equal volume) of the prescription isodose volume and $R_{eff, 50\%PD}$ (cm) is the effective radius of the 50% isodose line.

As a parameter related to side effects on the brain in SRS procedures, QUANTEC[7] recommends the adoption of the "volume receiving 12 Gy" (V_{12}). We also evaluated the ID to the brain, defined by equation 4[26] as the product between the mean dose to the brain ($D_{mean,\ brain}$) expressed in Gy and the brain volume (V_{brain}) expressed in liters.

$$ID = D_{mean\ brain}\left(Gy\right).V_{brain}(L) \quad (4)$$

In order to compare our data with the published literature, we considered the whole brain, including GTVs.[6]

Risk of brain radionecrosis evaluation

The risk for brain symptomatic radionecrosis for single fraction SRS to brain metastases rapidly increases once V_{12} >5–10 cc [Table 1].[6]

Such risk can be summarized with the model described by equation 5,[6] which calculates the normal tissue complication probability (NTCP) for radionecrosis as a function of V_{12}.

$$NTCP = \frac{1}{1+\left(\frac{V_{x,50}}{V_{12}}\right)^{4\gamma_{50}}} \quad (5)$$

Here, $V_{x,50}$ is the volume corresponding to 50% risk of necrosis and γ_{50} is the slope parameter. In this work we compared the results of such calculation for fixed/Iris and MLC plans. We used the best-fitting values found by Milano *et al*.[6] with the maximum likelihood method ($V_{x,50}$ = 63.2 cc, γ_{50} = 0.87).

Statistical analysis

The Shapiro–Wilk normality test for all the continuous variables was calculated. To explore the differences between continuous variables the Mann–Whitney or Student's *t*-tests were performed, as appropriate. The total target volume variable was categorized according to the median value, in order to explore the differences in NTCP values according to the PTV_{tot} value. Linear correlations between the two data sets were investigated by means of Spearman's correlation coefficient. Statistically significant $P < 0.05$ was considered. All statistical analyses were performed using SPSS statistical software version 21 (SPSS inc., Chicago IL, USA).

Graphical representations were obtained using MATLAB (The MathWorks Inc., Natick, MA) and RStudio (RStudio: Integrated Development for R. RStudio, PBC, Boston, MA) programming languages.

Results

All patients had 3–8 lesions (median 5) and the mean total target volume was (3.0 ± 1.8) cc, ranging from 0.8 to 6.8 cc.

For both fixed/Iris and MLC plans, QA verification with SRS MapCHECK system produced gamma pass rates above 90%.

The comparison between clinical and recalculated plans is summarized in Tables 2 and 3. The results are reported through mean with standard deviation and median with min – max range.

Table 1: V_{12} associated with risk of symptomatic radionecrosis, for single-fraction stereotactic radiosurgery to brain metastases[6]

V12 (cc)	Risk for symptomatic radionecrosis (%)
5	10
10	15
>15	>20

V_{12}: Volume receiving 12 Gy

The results reported in Table 2 show that fixed/Iris clinical plans had significantly higher conformity, homogeneity, and gradient index values. V_{12} and NTCP were lower but with no statistical significance. However, we found that for PTV_{tot} <2.58 cc differences in NTCP were statistically significant [Table 3].

On the other hand, MLC recalculated plans had significantly lower treatment time, number of MUs, number of beams, and number of nodes.

Figure 1 shows Spearman's correlation heatmaps obtained for fixed/Iris plans [Figure 1a] and for MLC plans [Figure 1b].

For both datasets, we found a high correlation between treatment time and number of lesions [Figure 2a], and between number of MUs and number of lesions [Figure 2b], with Spearman's correlation coefficients $r \geq 0.7$.

No correlation between treatment time or number of MUs and total target volume was found ($r < 0.3$).

For MLC plans only, a correlation between ID and number of MUs was found ($r = 0.7$).

We found a high correlation between V_{12} and the total target volume, with a Spearman's correlation coefficient $r = 0.9$ for fixed/Iris plans and $r = 0.8$ for MLC plans [Figure 3a]. Only a moderate correlation ($r = 0.6$) between V_{12} and the number of lesion for MLC plans was found, while for fixed/Iris plans no correlation was found.

A high correlation between DGI and V_{12} or ID was found, with a Spearman's correlation coefficient $r \geq 0.9$ for fixed/Iris plans and $r \geq 0.7$ for MLC plans [Figure 3b]. We also found a high correlation between DGI and the number of lesions for both groups of plans ($r = 0.7$ for fixed/Iris plans and $r = 0.9$ for MLC plans). No correlation between V_{12} and CN or HI was found.

Discussion

In this retrospective study, we compared CyberKnife plans calculated with fixed/Iris collimators and MLC collimator for nineteen patients affected with brain multiple metastases. We found that the two groups of plans provide dosimetric and beam delivery parameters that are different, however statistical significance ($P < 0.05$) in the difference was not observed in all cases. Fixed/Iris plans were characterized by significantly higher values of CN, HI, and DGI. However, as confirmed by the radiation oncologist, the recalculated MLC plans were clinically acceptable as well, according to AAPM TG-101.[18]

MLC recalculated plans had significantly lower CN (−8.6%) and HI (−2.2%). Regarding brain toxicity, a lower CN should be associated with a higher risk of complications because of a larger inclusion of normal tissue in the prescription volume, but we were not able to see this effect in our data as a correlation between CN and V_{12} which is the parameter related to brain

Table 2: Comparison between the results obtained with fixed/Iris clinical plans and multileaf collimator recalculated plans ($P<0.05$)

	Fixed/Iris		MLC		*P*
	Mean±SD	Median (range)	Mean±SD	Median (range)	
CN	0.76±0.08	0.75 (0.52–0.89)	0.70±0.11	0.70 (0.47–0.87)	0.042†
HI	1.14±0.02	1.15 (1.09–1.18)	1.12±0.02	1.12 (1.10–1.16)	<0.001†
DGI	32.98±17.84	30.29 (7.13–64.24)	18.47±19.32	16.57 (−10.33–48.02)	0.021*
V_{12} (cc)	17.79±8.79	14.96 (5.20–37.18)	22.09±8.82	21.13 (9.03–42.48)	0.141*
ID (GyL)	0.19±0.08	0.18 (0.01–0.32)	0.26±0.08	0.29 (0.12–0.40)	0.012*
NTCP	2.42±3.45	0.66 (0.02–13.63)	4.00±4.96	2.16 (0.11–20.06)	0.148†
Time (min)	46.05±7.80	47.00 (31.00–57.00)	37.58±7.49	36.00 (22.00–49.00)	0.002*
MU	18,257.96±5824.99	19,563.80 (8500.20–27,122.60)	12,175.18±4716.17	12,529.90 (4784.60–19,490.50)	0.001*
Nodes#	73.37±12.54	75.00 (55.00–94.00)	57.74±11.72	58.00 (33.00–77.00)	<0.001*
Beams#	121.16±28.05	121.00 (75.00–167.00)	65.47±15.09	66.00 (33.00–96.00)	<0.001*

*Student's *t*-test, †Mann–Whitney's test. Results are expressed as mean±SD and median (range). CN: Conformity, HI: Homogeneity, DGI: Dose gradient index, V_{12}: Volume receiving 12 Gy, ID: Integral dose, NTCP: Normal tissue complication probability, MU: Monitor units, MLC: Multileaf collimator, SD: Standard deviation

Table 3: Comparison between the normal tissue complication probability for radionecrosis obtained with fixed/Iris clinical plans and multileaf collimator recalculated plans, according to total planning target volume values

	Fixed/Iris		MLC		*P**
	Mean±SD	Median (range)	Mean±SD	Median (range)	
PTV_{tot} ≤2.58 (*n*=10)	0.34±0.26	0.26 (0.02–0.71)	1.34±1.35	0.90 (0.11–4.35)	0.045
PTV_{tot} >2.58 (*n*=9)	4.74±3.91	5.04 (0.62–13.63)	6.95±5.89	5.18 (0.85–20.06)	0.363

*Student's *t*-test. Results are expressed as mean±SD and median (range). PTV: Planning target volume, PTV_{tot}: Total PTV, MLC: Multileaf collimator, SD: Standard deviation

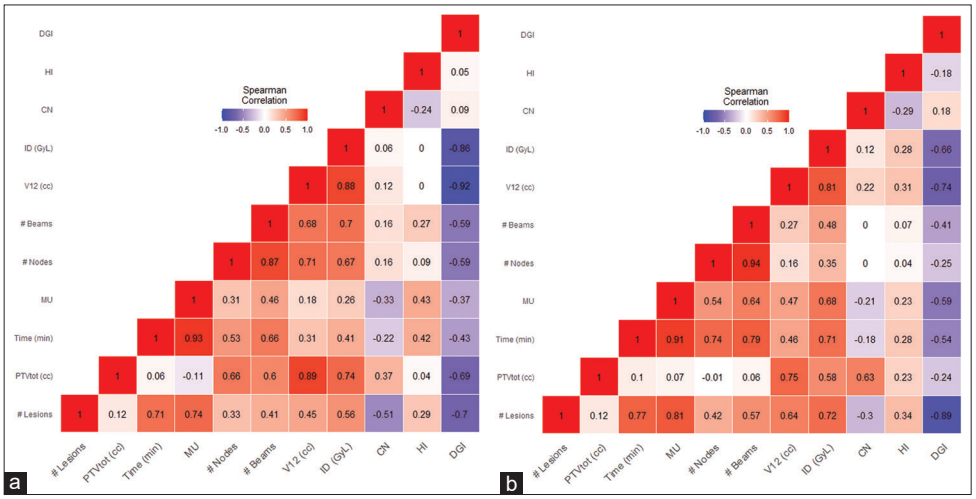

Figure 1: Spearman's correlation heatmaps obtained for (a) fixed plans and for (b) MLC plans. MLC: Multileaf collimator

toxicity. However, since V_{12} refers to a dose that is around 60% of our 21 Gy prescription, such a low isodose does not contribute to CN.

Inhomogeneous dose distributions result in higher doses within the target only, therefore they should not lead to an increased risk of complication probability, however, the effect of dose heterogeneity within the target on complication probability remains unclear in literature.[27] In our patient dataset, due to the constraint on the maximum allowed dose of our clinical protocol, the variability of HI was almost nonexistent both in fixed/Iris and MLC plans. Indeed, due also to the small number of patients, no correlation was found between HI and most of the other parameters, including V_{12}.

MLC plans yielded significantly lower DGI values (−44.0%) and higher ID (+35.9%). Actually we found much lower than ideal DGI values also for fixed/iris plans. In particular, we found that the higher is the number of lesions the lower is the DGI value for both groups of plans and especially for MLC plans. However,

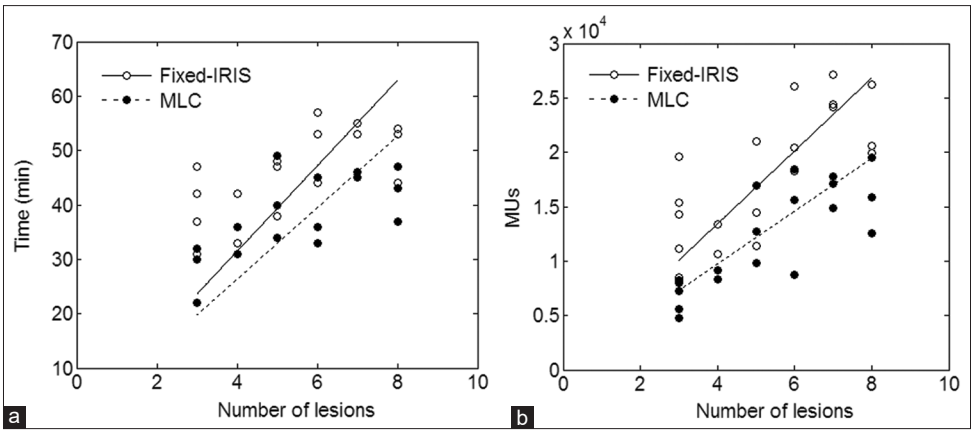

Figure 2: Correlation between (a) the treatment time and the number of lesion, and (b) the number of MUs and the number of lesion, for both datasets. MUs: Monitor units

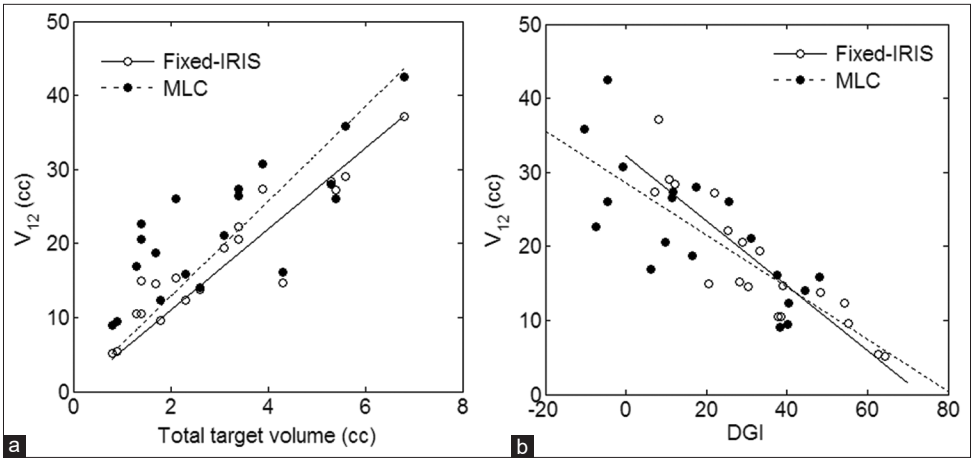

Figure 3: Correlation between (a) V_{12} and PTV_{tot} and between (b) V_{12} and DGI, for both datasets. DGI: Dose gradient index, PTV_{tot}: Total planning target volume, DGI: Dose gradient index

in multi-target cases meeting ideal DGI criteria is challenging due to abutting 50% of the R_x isodose lines between lesions, as reported by Reynolds.[14] In our study, we found a high correlation between DGI and V_{12} or ID, showing that DGI influences the volume of healthy brain tissue receiving radiation dose. The lower DGI values of MLC plans corresponded to higher V_{12} or ID values, with respect to fixed/Iris plans. This translated in wider dose distributions for MLC plans, as shown in Figure 4.

In general, the ID of the brain depends on a number of factors. As reported by D'Souza[28] beam margin size and beam energy are the most relevant parameters. Smaller margins and higher energies reduce the ID, regardless of the number of nodes or beams involved. In the present study, beams with the same energy (6MV FFF) were delivered, but it can be assumed that the beam margin size provided by MLC leaves was wider, with respect to fixed or Iris collimators, as shown in Figure 5.

The wider penumbra could also be associated with the lower CN and HI values registered in MLC plans. In fact, a wider margin produces less conformed prescription isodose lines around the target and more homogeneous dose distributions within the target. Our results are in agreement with Jang *et al*.,[29] which reported that targets with a size less than the minimum MLC opening (i.e., 7.6 mm × 7.5 mm) might not be good candidates for MLC-based planning.

Petti *et al*.[30] showed that the peripheral dose in CyberKnife brain radiosurgery is largely related to radiation leakage. They found that the dose leakage was 2–5 times higher than that measured for a comparable Gamma Knife treatment. Despite the higher number of MUs (+33.3%), for fixed/Iris plans the ID to the brain was much lower. Actually, we found no correlation between ID and number of MUs for fixed/Iris plans, while for MLC plans a positive correlation was found. The wider dose distributions and the higher ID values of MLC plans could be also associated with the 0.5% transmission factor of the MLC leaves,[31] much higher than fixed/Iris collimators.

It should be also noted that, in our study, the mean V_{12} values obtained were doubled with respect to the generally recommended 10 cc threshold for single lesion SRS[32] (17.8 ± 8.8 cm^3 for fixed/Iris plans and 22.1 ± 8.8 cm^3 for MLC plans). This is a consequence of the high number of lesions treated for each patient. An issue specific to multi target

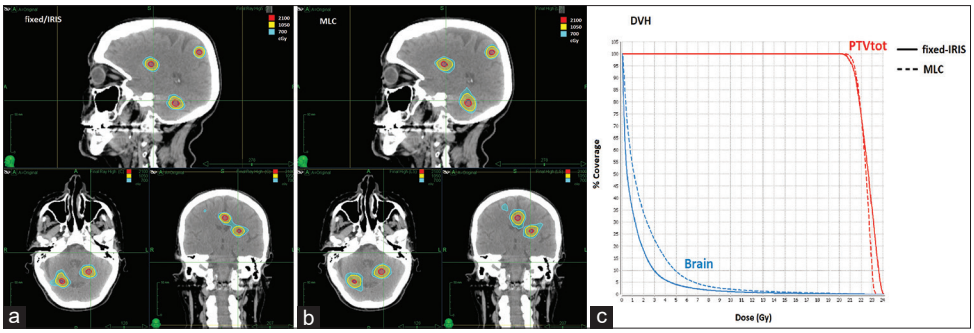

Figure 4: Dose distribution comparison between (a) MLC and (b) fixed/Iris plans, for a representative patient; (c) DVH comparison between fixed/iris (solid line) and MLC (dashed line) plans for the same patient. MLC: Multileaf collimator, DVH: Dose Volume Histogram

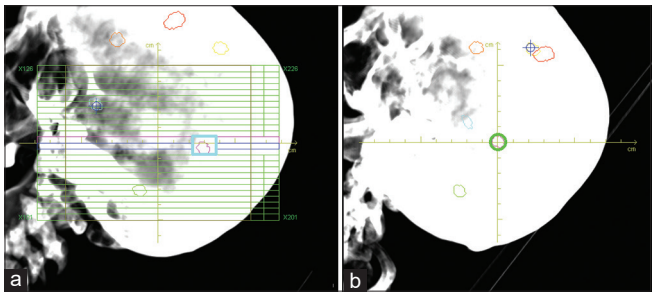

Figure 5: BEV comparison between (a) MLC and (b) fixed/Iris plans, from a similar node. The margin around the same metastasis is highlighted by a cyan rectangle for MLC and by a green circle for fixed/Iris collimator. MLC: Multileaf collimator, BEV: Beam Eye View

SRS, on which further investigations should be performed, is whether the V_{12} and the risk of necrosis are reported for single lesions or for the total target volume.

On the basis of the study by Milano *et al*.,[6] we estimated the NTCP for symptomatic radionecrosis as a function of V_{12}. The authors highlighted that the logistic model used for NTCP should be considered only as a descriptive way to summarize the data and not intended to be predictive. In this work, we wanted to give an estimation of NTCP, but we are aware that our results should be validated on the basis of clinical follow-up.

In our study, no correlation was found between the number of lesions and the total target volume. This may happen whenever the volume range of the lesions is sufficiently wide (in our data such range goes from 0.05 cc to 4.73 cc). For example, one of the patients with 3 lesions had a PTV_{tot} of 4.3 cc and one of the patients with 8 lesions had a PTV_{tot} of 3.9 cc. Our results showed that the total target volume may be more significant in terms of prognosis rather than the number of lesions since we found a high correlation ($r \geq 0.8$) between V_{12} and the total target volume for both datasets [Figure 3a]. Only a moderate correlation ($r = 0.6$) between V_{12} and the number of lesion was found for MLC plans. These results are in agreement with other studies in the literature,[33-35] showing that the target volume, unlike the number of metastasis, can be associated with the overall survival, and the absence of neurologic symptoms related to radionecrosis can be significantly associated with the longer overall survival.

Our results showed that the difference in NTCP estimated for the two groups of plans becomes statistically significant ($P < 0.05$) when PTV_{tot} is less than the median value of 2.58 cc [Table 3]. This could be explained considering that the MLC beam penumbra is generally wider and could produce more spread-out dose distributions in the surrounding tissues, as also shown by the significantly higher values of ID. For smaller target volumes this effect could be much more consistent. Therefore, if the total target volume is above this threshold, fixed/Iris and MLC plans may be considered equivalent in producing a given toxicity risk. In this case, delivering an MLC plan could be beneficial. The main advantage provided by MLC plans is that all beam delivery parameters are significantly lower than those given by fixed/Iris plans. In our study, treatment times were on average 18.4% shorter and the number of MUs was on average 33.3% lower. The reduction in the number of MUs resulted also in the reduction of the number of beams (−46.0%) and nodes (−21.3%). We found that the treatment time, the number of MUs, and therefore the treatment duration, were correlated with the number of lesions rather than the total target volume. This could be explained considering that the higher the number of lesions, the higher will be the number of nodes and the time spent by the robot to position between nodes, because of lesions spread.

Treatment time reduction could represent an important advantage for not compliant patients, even if the treatment consists of only one fraction. In our study, the treatment time of fixed/Iris plans was on average 46.1 min, while for MLC plans it was 37.6 min. For painful patients even an extra minute can make a difference, however, treatment time should not be considered the main factor when evaluating a CyberKnife plan. If the total target volume is <2.58 cc, delivering a MLC plan may increase the risk for brain radionecrosis.

To briefly investigate whether a relaxation of the maximum dose constraint could positively affect our results, we re-optimized a few pairs of fixed/Iris vs. MLC plans, removing said constraint. The mean prescription isodose of the resulting plans dropped to 67% for fixed/Iris but remained around 84%

for MLC plans. A noteworthy decrease in V_{12} and increase in DGI was found for fixed/Iris plans only, while the effect on treatment time was marginal in both plan classes. Perhaps, modifying other parameters could produce better MLC plans, but it could also increase the overall treatment time. The clinician should evaluate on a case-by-case basis if the shorter treatment time of MLC plans may be an advantage when treating multiple small spherical targets. If the treatment time of an MLC plan is comparable to or longer than the treatment time of a fixed/Iris plan, we suggest to choose the fixed/Iris plan, as the ID values were found to be significantly lower, in order to produce dose distributions with steeper gradients and better sparing of surrounding normal tissue. A background limitation to this line of reasoning is the absence in the literature of a universally accepted set of parameters for the assessment of dose distributions against adverse effect on brain tissue when treating multiple metastases.

Conclusions

CyberKnife MLC plans for stereotactic treatment of brain multi-metastases could be considered clinically acceptable and could provide an important advantage for the patient in terms of treatment time. However, fixed/Iris plans are characterized by significantly better dosimetric parameters that can influence the NTCP for radionecrosis, in particular for total target volumes <2.58 cc. Therefore, MLC plans could be competitive for patients with larger total target volumes. The final choice must be obviously based on clinical considerations.

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Conflicts of interest

There are no conflicts of interest.

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