

# Benefit of dosimetry distribution for patients with brain metastases from non-small cell lung cancer by Cyberknife Stereotactic radiosurgery (SRS) system

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## Research article

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# Abstract

## Background

To pursue high precision in tumor and steeper dose fall-off in healthy tissues of brain metastases stereotactic radiosurgery (SRS), this study investigated an optimized planning by comparison only one multiple-lesions-plan (MLP) and multiple single-lesion-plans (SLP) in the treatment of brain metastases using Cyberknife (CK) Robotic Radiosurgery System.

## Methods

Fifty non-small cell lung cancer (NSCLC) patients (28 males and 22 females) with 2-4 multiple brain metastases were retrospectively replanned with 12 to 32 Gy prescription dose in 1 to 3 fractions. Two different clinical SRS plans (SLP and MLP) for the same patients were generated, under the same collimator and prescription isodose line (62-68%) by CK Multiplan System. Both the SLP and MLP were able to get ≥95% PTV volume covered prescription isodose and meet the Timmerman 2011 OAR (brainstem, optic nerve and pituitary) constraints.

## Results

Compared with the SLP, the maximum dose ( $D_{max}$ ) and mean dose ( $D_{mean}$ ) of brainstem in the MLP decreased 0.22-3.13% (2.62%) and 2.71-12.56% (5.57%), over all  $P \leq 0.05$ . While the volumes of whole brain minus the tumors received a single dose equivalence of 8-16Gy ( $V_{8Gy}$ - $V_{16Gy}$ ) could effectively reduce in the MLP. And the treatment time parameters (the total number of beams and monitor units (MU)) of the MLP declined 3.31% and 1.47% ( $P \leq 0.05$ ) respectively. Although there were a few differences of conformity index (CI) and homogeneity index (HI) between two treatment plans, it was no statistical significance ( $P = 2.94$  and  $1.08 \geq 0.05$ ).

## Conclusion

One multiple-lesions-plan for brain metastases could achieve higher precision in target and lower dose in healthy tissue, while shorten the treatment time and improve the treatment efficiency.

## Background

Brain metastases develop in 20–40% cancer patients, which include 36–64% patients with lung cancer, 15–25% patients with breast cancer, a few of patients with melanoma, colorectal cancer and renal carcinoma [1, 2]. Clinical treatment options for patients with brain metastases included surgery, whole brain radiotherapy, stereotactic radiosurgery (SRS) alone or in combination [3]. Although the whole brain radiotherapy (WBRT) can improve the control rate of multiple brain metastasis, it cannot prolong the overall survival of the patients, and it increases toxic side reaction risk of the patients' nervous system [4–6]. While SRS alone or combined with immunotherapy can guarantee the curative effect and avoid the patients' long-term adverse reaction of clinical treatment. Therefore, it has been recognized and accepted

by more and more clinical experts and patients, and it has gradually become the core protocol to treat multiple metastases.

American national comprehensive cancer network (NCCN) recommend SRS for patients with brain metastases, included: 1) Diameter of tumors < 5 cm, 2) Number of tumors  $\leq 4$ , 3) Combined with surgery or WBRT, 4) Recurrence after SRS (6 months) [7]. The common SRS treatment equipment concludes Gammaknife, Cyberknife (CK) and various kinds of linear accelerator [8, 9]. CK can be used to treat encephalic lesions by adopting orthogonal X-ray tubes to image patients' heads in real time and performing radiotherapy of encephalic lesions by positioning through skull registering of patients. Therefore, CK SRS can improve the dose in the tumor and reduce injury of healthy brain tissue as well [10].

In addition to local control, remote control and overall survival rate Furthermore, various nervous functional states and living quality should be focused on for brain metastases treatment. CK SRS adopts single large-segmentation radiotherapy for treating the patients with multiple brain metastases. That easily results in more radiation dose absorbed by normal brain tissue and organ at risk (OAR) adjacent tumor and increases the probability of clinical encephaledema, intratumoral tardive bleeding or brain necrosis, etc [11, 12]. Therefore, how to effectively reduce irradiation dose absorbed by normal brain tissue is essential for CK SRS treatment planning.

Single-lesion-plan (SLP), which is one-on-one treating for SRS plans and tumors, often used during CK SRS planning for patients with multiple metastases. In this paper, we attempted to develop a multiple-lesions-plan (MLP), which was using only one plan for multiple brain metastases treatment. Retrospective analysis and evaluation were made on the quality, efficiency and difference of dose distribution between CK SRS SLP and MLP for 50 non-small cell lung cancer (NSCLC) patients with multiple metastases in the CK center of Tianjin Medical University Cancer Hospital, so as to provide a certain reference basis for design of CK SRS treatment plan clinically.

## Methods

### Patients and simulation

This retrospective study included 50 NSCLC patients (median (range) age 64 (45–78) years, 28 male and 22 females) with 2–4 brain metastases treated by CK SRS with 12 to 32 Gy prescription dose in 1 to 3 fractions at our institution. 114 lesions (median volume (range) 0.85 to 9.62 cc (4.72 cc) were included in this study. The patient details are listed in Table 1, 39 patients with 2 brain metastasis, 8 patients with 3 brain metastasis and 3 patient with 4 brain metastases. The study was approved by our ethics committee wrote informed consent provided by the patients.

Table 1  
50 Patient characteristics

|                     |         | Number (%) |
|---------------------|---------|------------|
| Target number       | 2       | 39 (78%)   |
|                     | 3       | 8 (16%)    |
|                     | 4       | 3(6%)      |
| Target volume(cc)   | ≤1 cc   | 23 (20.2%) |
|                     | 1–5 cc  | 84 (73.7%) |
|                     | 5–10 ml | 7 (6.1%)   |
| Tumor diameter (cm) | ≤1 cm   | 26 (22.8%) |
|                     | 1–3 cm  | 77 (67.5%) |
|                     | ≥3 cm   | 11 (9.6%)  |

Overall skull CT scan for the patients was performed by Philips Brilliance Big Bore CT (16 rows), with the thickness of scan layer of 1.5 mm. T1-weighted magnetic resonance imaging scan with Siemens 1.5 was registered to CT. And the gross tumor volume (GTV) delineates with the fusion images. A 1.6-mm margin was added to the GTV to create the plan tumor volume (PTV).

## CK SRS treatment planning

Five dose-limiting shells (2 mm, 3 mm, 5 mm, 7 mm, 9 mm) away from the each PTVs were created to optimize the dose distribution to healthy brain tissues. Based on the delineation results and requirements, the planner conducted the design and optimization of the CK SRS plans by adopting the through the CK MultiPlan system. Two different treatment plans were designed for every patient, included SLP (one plan to one PTV) and MLP (one plan for all PTVs). The same collimator and prescription isodose (65–70%) were adopted during plans designing for the same patient, without the iris or MLC system, in order to ensure the consistency of beam data in plans. A high-resolution calculation step was performed in the evaluation step to finalize the CK SRS plans. All the planes were able to meet ≥95% coverage of the PTV with prescription dose and the Timmerman 2011 OAR (brainstem, optic nerve and pituitary) constraints [13]. Radiotherapy path was forbidden to pass through patients lens in the CK SRS plans, so that the maximum dose for the lens ≤1 Gy.

## Data analysis

The same patient's SLP should be superimposed and evaluated by the comparison of dosimetry distribution in metastatic tumors, normal brain tissue and OAR. The conformity index (CI) represents the objective measure of how well the distribution of radiation follows the shape of the PTV, and calculated as follows:

$$CI = PIV/TIV (1)$$

Where PIV was the volume included by prescription isodose, and TIV was the tumour volume covered by prescription isodose volume. This definition of CI is different than the radiation therapy oncology group (RTOG) definition, which is PIV divided by total tumor volume [14]. The closer the value of CI is to 1, the better the plan.

In order to quantify the difference of dose parameter, the value of minimum dose ( $D_{\min}$ ), maximum dose ( $D_{\max}$ ) and covering mean dose ( $D_{\text{mean}}$ ) for healthy brain tissue and OAR were expressed as percent of the global maximum dose in plans. And the reduction of them will be calculated as follows:

$$R = (\text{Data}_{\text{SLP}} - \text{Data}_{\text{MLP}}) / \text{Data}_{\text{MLP}} \quad (2)$$

Where  $\text{Data}_{\text{SLP}}$  and  $\text{Data}_{\text{MLP}}$  represented the value of SLP and MLP respectively.

Furthermore, the volumes of whole brain, minus the PTVs, received a single dose equivalence of 4 to 16 Gy (V4Gy-V16Gy) were evaluated by assuming  $\alpha/\beta$  ratio of 2.0 to brain tissue with iLQ (V4.0) [15]. The total number of beam and monitor units (MU) were compared.

All statistical analyses were performed with SPSS (the Statistical Product and Service Solutions for Statistical Computing, IBM, USA, version 19.0). Data from different plans were compared with a two-sided paired t test. P-value < 0.05 was considered statistically significant.

## Results

Figure 1 was the dosimetry distribution of MLP versus SLP for the same patient with two brain metastases. The results illustrated that, the radiation around the PTV was more divergent in the SLP, for example, the 40% isodose (purple line) was included in the PTV + 6 contour in MLP (as shown in Figure.1(B)), but not in SLP (as shown in Figure.1(C)). While the OAR (brainstem) got very well protected and characterized as less irradiated areas, the 10% isodose did not appear in the brainstem from MLP. These illustrated that using MLP for patients with multiple brain metastases could significantly reduce dose distribution in healthy brain tissue and OAR.

In order to quantify the difference of dosimetry distribution, the statistical analysis of CK SRS plans for 50 patients was shown in Table 2. The value of  $D_{\min}$ ,  $D_{\max}$  and  $D_{\text{mean}}$  were expressed as percent of the global maximum dose in plans. The dose in the PTV + 6 significantly decreased in MLP,  $D_{\max}$  value dropped 0.29–1.91%,  $D_{\text{mean}}$  value decreased 1.89–2.58%,  $D_{\min}$  value dropped 4.35–8.98%. And dose parameters of OAR were in Table 2. MLP could decrease the radiation dose in OAR, especially  $D_{\max}$  and  $D_{\text{mean}}$  value of brainstem decreased 0.22–3.13% and 2.71–12.56%. These meant using MLP for multiple brain metastases patients' treatment could reduce the risk of symptomatic radiation-induced injury in healthy brain tissue and OAR.

Table 2  
Dosimetric distribution of PTV + 6 and OAR in CK SRS SLP and MLP for 50 patient

|  |                   | SLP mean(range)      | MLP mean(range)      | R mean(range)      | t     | p    |
|--|-------------------|----------------------|----------------------|--------------------|-------|------|
| PTV + 6  | D <sub>Max</sub>  | 89.75%(80.20–93.90%) | 89.07%(79.99–92.11%) | 0.77%(0.29–1.91%)  | -1.00 | 0.04 |
|  | D <sub>mean</sub> | 54.69%(46.54–65.02%) | 53.18%(45.34–63.79%) | 2.34%(1.89–2.58%)  | 2.10  | 0.03 |
|  | D <sub>Min</sub>  | 35.46%(29.65–43.55%) | 33.82%(28.36–39.64%) | 4.62%(4.35–8.98%)  | 5.40  | 0.01 |
| Brainstem  | D <sub>Max</sub>  | 21.57%(18.15–23.76%) | 21.02%(18.49–23.04%) | 2.62%(0.22–3.13%)  | 2.15  | 0.03 |
|  | D <sub>mean</sub> | 11.49%(5.27–20.68%)  | 10.85%(4.45–20.12%)  | 5.57%(2.71–12.56%) | 1.18  | 0.01 |
| Optic Nerve  | D <sub>Max</sub>  | 14.10%(4.56–18.85%)  | 13.56%(4.44–18.57%)  | 2.63%(1.49–3.83%)  | 3.66  | 0.02 |
|  | D <sub>mean</sub> | 7.16%(5.18–10.02%)   | 6.88%(4.52–9.35%)    | 6.91%(3.69–12.74%) | -5.28 | 0.01 |
| Optic Chiasm   | D <sub>Max</sub>  | 14.90%(7.53–21.05%)  | 14.41%(7.47–19.93%)  | 3.29%(0.80–5.32%)  | -3.77 | 0.04 |
|  | D <sub>mean</sub> | 6.08%(3.21–8.96%)    | 5.92%(2.95–8.83%)    | 5.63%(1.45–8.10%)  | 6.07  | 0.01 |
| *PTV + 6 was 6-mm-thick zones of healthy brain tissue adjacent the PTV, D <sub>Max</sub> , D <sub>mean</sub> and D <sub>Min</sub> were maximum dose, mean dose and minimum dose, expressed as percent of the global maximum dose in plans. |                   |                      |                      |                    |       |      |

The statistical results of V4Gy-V16Gy were shown in Fig. 2. Although there was no obvious difference in V4Gy and V6Gy, V8Gy-V16Gy value had a marked decline in MLP. This finding provides more evidence for the theory that using the MLP could protect healthy brain tissue better while satisfying the need of clinical treatment.

Table 3 compared the CK SRS plan parameters. CI of the two different planning were close to each other, even without statistical difference. It indicated that the SLP or MLP could get better curative effect for targeted volume of patients clinically. While the total number of beam and monitor units were lower in MLP, with an average decrease of 4.63% and 0.56% respectively. Therefore, when the patients with multiple brain metastases were treated with CK SRS, the execution time of MLP was apparently less than the SLP.

Table 3  
Indexes of 50 patient CK SRS plans

|                          | SLP mean(range)                | MLP mean(range)                | R<br>mean(range)       | t     | P    |
|--------------------------|--------------------------------|--------------------------------|------------------------|-------|------|
| Conformity index (CI)    | 1.14<br>(1.04–1.23)            | 1.13<br>(1.03–1.24)            | /                      | 1.57  | 2.94 |
| Homogeneity index (HI)   | 1.35<br>(1.32–1.47)            | 1.37<br>(1.33–1.47)            | /                      | -4.21 | 1.08 |
| Total beam number        | 133<br>(101–149)               | 128<br>(97–138)                | 3.96%<br>(3.76–6.71%)  | -1.71 | 0.01 |
| Total monitor units (MU) | 12774.83<br>(9121.67-15243.74) | 12719.26<br>(8974.16-15158.49) | 0.56%<br>(0.43%-1.64%) | 1.09  | 0.04 |

## Discussion

With the improvement of medical technology and increasingly prolonging of lifetime of cancer patients, brain metastasis has already become one of importantly clinical manifestations for late cancer patients. Some researchers have shown that about 80%

patients with brain-metastases could have 1–3 metastases tumors simultaneously [16]. At present, treatment ways for brain-metastases tumor mainly include surgical operation, WBRT, SRS, etc. [17]. Chang, et al. believed that compared with the WBRT, SRS could increase local control rate of intracranial tumors, avoid the occurrence of long-term nerve cognitive disorder and improve patients' living quality [18]. Rades Dirk, et al. made a retrospective comparison and analysis on patients with brain metastases treated by SRS or WBRT (the tumors number  $\geq 3$ , and the tumor diameter  $\geq 4$  cm), the results showed that the meso-position lifetime and one-year local control rate in SRS group were superior than WBRT group [19, 20]. Chung C, et al. indicated that 68% radiation oncologists believed 1–3 brain metastases was ideal quantity to be treated with stereotactic radioactive surgery (SRS) [21]. Murovic Judith, et al. made a comparison and analysis on patients with 1–3 brain metastases and on the curative effect for more than patients with 4 brain metastases who only received CK SRS, the results showed that the meso-position OS for both were 13 months, without apparent difference, therefore CK radiosurgery could effectively control the patients with brain metastases [22].

For treatment of multiple brain metastases, CK SRS can effectively shorten treatment cycle and time. As a result, severe radiation damage in the clinic can be avoided. Additionally local control rate of patients' lesions can be improved. In this study, analytical research was made on 50 patients with multiple brain metastases treated by SLP and MLP from CK SRS system. The results showed that the MLP could ensure that the prescription dose covered PTV, effectively reduced dosage distribution of healthy brain tissue and OARs. CI indexes of SLP and MLP for the same patients were similar, without statistical difference. That

meant these two different plans could lead to relatively ideal dose distribution for PTV. Compared with the SLP, MLP could effectively shorten treatment time with less number of treatment nodes and total machine hops. Therefore, it indicated that the MLP can be used for good clinical treatment of patients with multiple brain metastases by CK SRS.

It's worth noting that multiple collimator (collimators number  $\leq 3$ ) combination is needed to be selected to realize MLP for CK SRS treatment, when the patient has different size and volume metastasis lesions. But technician is needed to change the collimators when the third generation or lower version of the CK system (G3) to implement clinical treatment, which causes a certain complication and extension of treatment time. Therefore, both convenience and safety of clinical operation should be comprehensively considered during CK SRS planning.

In a word, when CK SRS is used for clinical treatment of patients with multiple brain metastases, adopting MLP can ensure dose distribution and curative effect, effectively reduce radiation injury of patients' normal brain tissue and normal tissue, shortening time of clinical treatment. CK SRS plans are designed for patients with multiple brain metastases, dose distribution and clinical treatment time should be fully considered. While the clinical curative effects for both plan designs are required to be further discussed through collecting and tracing more cases, so as to establish reliable clinical database, providing more significant reference for implementation of treatment.

## Conclusion

The results of this study demonstrated that the multi-lesions-plan, with less total number of beam and monitor units, was significantly reduced radiation injury outside the tumors, compared with the SLP. The resultant the maximum dose ( $D_{max}$ ) and mean dose ( $D_{mean}$ ) value of OAR (brainstem) in the MLP was significantly lowered. Only one multiple-lesions-plan can meet the needs of SRS treatment for multiple brain metastases, deliver large dose to the tumor and achieve minimizes the amount of radiation delivered the healthy tissues.

## Abbreviations

SRS: Stereotactic radiosurgery; WBRT: Whole brain radiotherapy; NCCN: national comprehensive cancer network; CK: Cyberknife; OAR: Organ at risk; SLP: Single -lesion-plan; MLP: Multiple-lesions-plan; NSCLC: Non-small cell lung cancer; GTV: Gross tumor volume; PTV: Plan tumor volume; CI: Conformity index; RTOG: Radiation therapy oncology group;  $D_{min}$ : Minimum dose;  $D_{max}$ : Maximum dose;  $D_{mean}$ : Covering mean dose for healthy brain tissue; V4Gy-V16Gy: Received a single dose equivalence of 4 to 16Gy; MU: Monitor units.

## Declarations

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### **Authors' contributions**

Study concept and design: YXY, WP. Acquisition, analysis, or interpretation of data: WYW. Drafting of the manuscript: YXY, YH. Critical revision of the manuscript for important intellectual content: ZLJ, YZY. Statistical analysis: WYW, SYC. Obtained funding: YXY, WP. Administrative, technical, or material support: YZY. Study supervision: ZLJ. All authors read and approved the final manuscript.

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### **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Ethics approval and consent to participate** Patients gave verbal informed consent to participate at time of diagnosis and the ethics committee at Tianjin Tumor Hospital approved this procedure (Ek2019037). Patients were informed that they had the opportunity to opt-out if they were not willing to participate in the study.

### **Consent for publication**

Not applicable

### **Competing interests**

The authors declare that they have no competing interests.

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## Figures

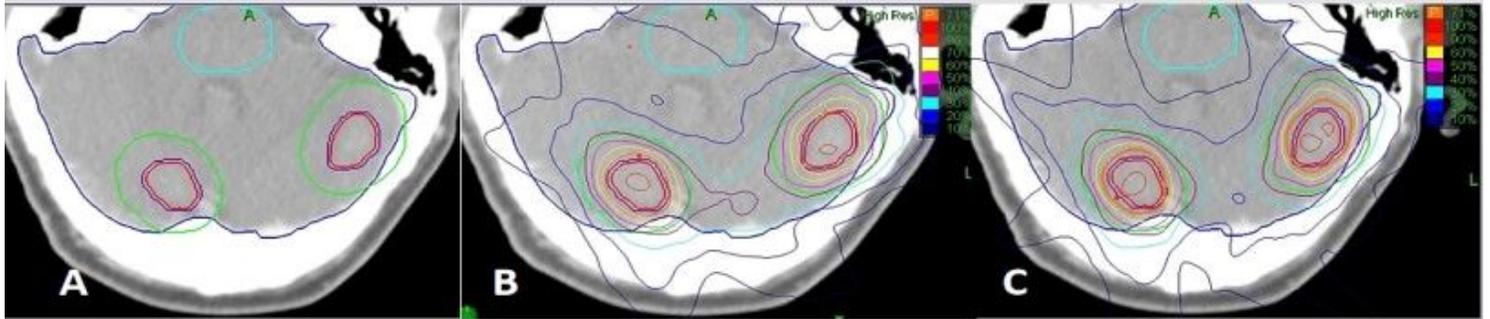


Figure 1

Different CK SRS plans for the same patient with multiple brain metastases. The representative patient had axial images taken, (A) shown the location of the tumors (red line area), healthy brain tissue around the PTVs (green line area), the whole brain (blue line area) and OAR (Light blue line area was brainstem), (B) and (C) were single-lesion-plan (SLP) and multi-lesions-plan (MLP). The red and purple lines indicate the GTV and the PTV, respectively. Black and blue lines represent brain tissue and brainstem. Green contour was covered with 6-mm thick zone adjacent to the PTV. Isodose: Orange-Prescription dose, Red-100% and 90%, White-70%, Yellow-60%, Pink-50%, Purple-40%, Blue represents 10 to 30 from light to deep, respectively.

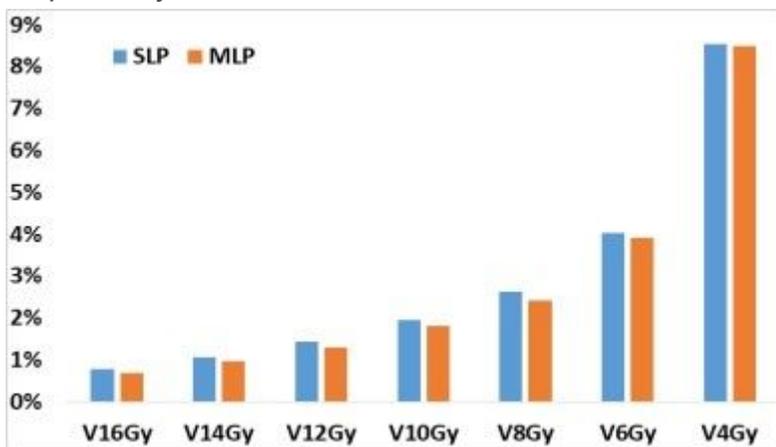


Figure 2

The statistical results of V4Gy-V16Gy in the whole brain tissue excluding the PTVs.