International Journal of Medical Physics, Clinical Engineering and Radiation Oncology, 2022, 11, 113-123
https://www.scirp.org/journal/ijmpcero
ISSN Online: 2168-5444
ISSN Print: 2168-5436

Distance to Isocenter Directly Affects Margin and Inappropriate Margin Increases the Risk of Local Control Failure in LINAC-Based Single-Isocenter SRS or SRT for Multiple Brain Metastases

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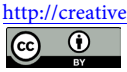
How to cite this paper: Gao, J.F. (2022) Distance to Isocenter Directly Affects Margin and Inappropriate Margin Increases the Risk of Local Control Failure in LINAC-Based Single-Isocenter SRS or SRT for Multiple Brain Metastases. *International Journal of Medical Physics, Clinical Engineering and Radiation Oncology*, **11**, 113-123.
https://doi.org/10.4236/ijmpcero.2022.112010

Received: April 12, 2022
Accepted: May 21, 2022
Published: May 24, 2022



Abstract

In the advancement of single-isocenter multiple target treatment in the LINAC-based SRS or SRT, the target distance to the isocenter and grouping of multiple targets are the highly concerned and debatable topics in the SRS/SRT field at present. Three failure and success cases of local control in our early practices are presented in this study and it indicated that the target distance to the isocenter directly affects the margin and an inappropriate margin increase the risk of local control failure. The GTV expansion margin should be LINAC-specific and institute-specific. Within the physics and dosimetry scope, the AHARA (as high as reasonably achievable) principle is the first time proposed to the radiation oncology field. Radiobiology and tumor response complexity is beyond this study.

Keywords

Single-Isocenter Multiple Target, SRS/SRT, AHARA, Winston-Lutz-Gao Test

1. Introduction

After several decades' standard care of whole brain radiotherapy (WBRT) for brain metastasis treatment, stereotactic radiosurgery (SRS) has been becoming the new standard care to treat brain metastasis tumor (Met). This is attributed to several major clinical trials which aimed at limited un-resected brain metastasis from 2009 to 2015. Recently Mahajian and Brown [1] [2] have led two separate groups to perform phase III trial on the postoperative brain cavity SRS with ob-

servation and SRS with WBRT. They both conclude that the "SRS is safe and effective alternative to WBRT as postoperative treatment" [3]. Japan Clinical Oncology Group just finished one phase 3 random trail and concluded that SRS is non-inferior to WBRT for patients with one to four intact brain metastasis [4], as some researchers hailed that "The sun is setting on WBRT, and SRS is rising to be the standard of care" [5].

Sahgal. Arjun made a comprehensive review of SRS clinical outcome and technology development past decades [6]. Traditionally the SRS is very time-consuming, invasive and labor-intensive procedure for both patient and medical staff. The inventive single iso-multiple target treatment (SIMT) is a special Linac-based SRS technique that can treat multiple brain targets by a single-isocenter in a very efficient way comparing LINAC multi-iso, Gammar knife, or Cyberknife technique. It has been adopted by many institutes and clinicians worldwide. Joshua D. Palmer *et al.* [7] performed some studies and further proved that the single iso-multiple target is safe and effective technique. During the implementation of the single iso-multiple target (SIMT) technique, the accuracy of small field dosimetry and mechanical QA are two challenges to medical physics field. The latter one is more challenging because the gantry, collimator and couch axis rotational uncertainty not only depend on type of LINAC, the age of LINAC, frequency and accuracy of quality assurance (QA) of LINAC but also patient weight, number of Mets inside brain and how far the Met is offset from isocenter.

There are many studies on radiobiology, treatment schema, planning technique, LINAC QA, image guidance, etc. in the SIMT procedure. One debatable study is the one which was performed by one group from university hospital of Zurich [8]. They perform the SIMT on LINCA TrueBeam or Edge (Varian Medical Systems, Palo Alto, US) LINAC with a high definition multi-leaf collimator (MLC). A pre-defined 1 mm margin was used in their fancy LINAC; a statistical model was used to generate data. Per the limited research from only two university hospitals and one type of LINAC, then they conclude that the distance to isocenter is not associated with an increased risk for local control failure in SIMT. They neglected the quality difference among different LINACs and quality assurance difference among different institutes. This will potentially give some radiation oncologists and medical physicists the wrong perception that SIMT is a quick and easy way to treat brain Mets regardless of where the Met is located. This will potentially cause more local control failure in the LINAC-based SIMT procedure.

In this study, we presented three failures or successes of local control SIMT cases with different targets to iso distance in our early practice. These three cases were randomly selected from about 25 patients we treated in the first year by new machine in one free-standing clinic. Mets numbers ranged from 2, 3 and 4 spread out in the whole brain. We followed some university hospital guidelines at the beginning. The same uniform margin was used in the group in university hospital of Zurich. Two of them failed in the local control in which a single-isocenter was used to treat large distance (between target and isocenter) targets. One of them was successfully controlled in which two isocenters were used

to treat a large distance target. Beyond the complexity of radiobiology and tumor response, the inappropriate margin caused by a large target to isocenter distance is a highly suspicious factor of local control failure. All three cases are elaborated from the planning to treatment whole process in the following. It reflected some good and bad experiences in our very early learning period. There is no statistical model or error involved. Our belief is that each cancer patient deserves the best care, and is not just a statistic number in the era of customized medicine. These three cases are very good exceptions to the findings by the group from university hospital of Zurich [8]. It brought some hint of analogy to the physics world in the early 20th century.

2. Materials and Methods

Patient A:

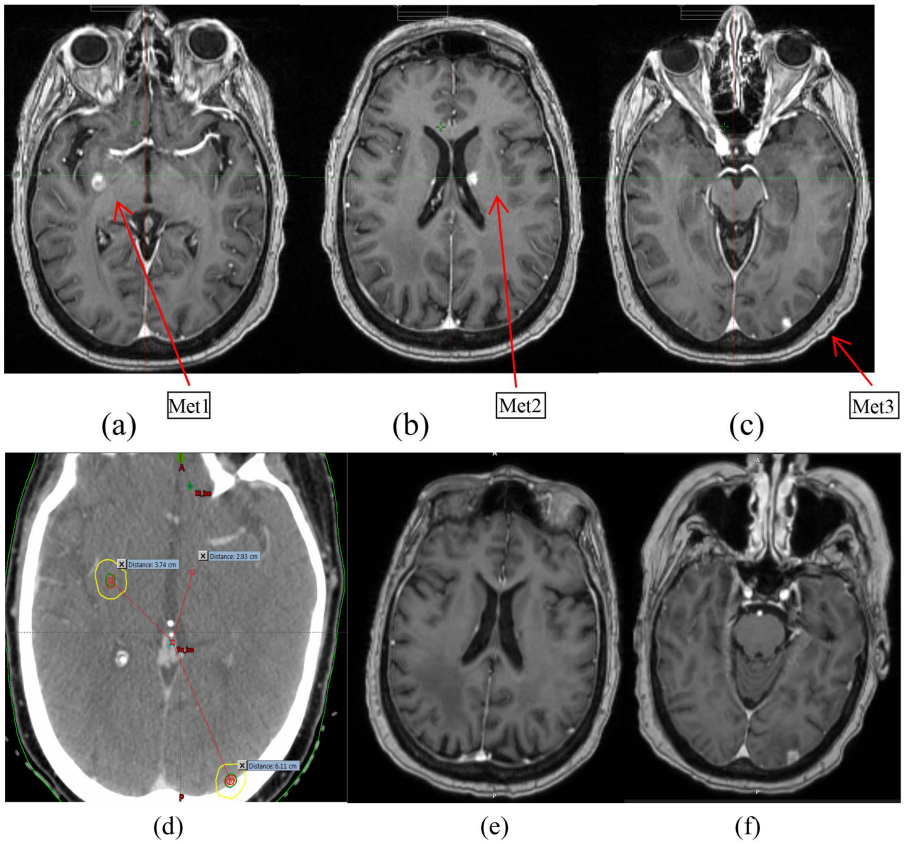


Figure 1. Mrs. A MRI images before treatment in (a), (b) and (c); Eclipse treatment plan isocenter placement diagram (d); Post treatment follow up MRI image for Met1 and Met2 (e); Post treatment follow up MRI image for Met3 (f).

Mrs. A is a 68-year-old woman who presented to the clinic with brain metastases and originally underwent a radical mastectomy on her right breast in September 2017. Later on, she received adjuvant chemotherapy and post-mastectomy radiation therapy in July 2018. After three months of treatment, she complained to her family doctor about dizziness, nausea and hard to balance during walking.

Then she underwent one MRI in October 2018 and showed those three diffuse brain metastases are presented with the largest one of 1.8 cm in the right cerebellum. Then whole brain radiation therapy (WBRT) was performed in November 2018. One PET scan in Feb 2019 indicated multiple metastases in liver and upper abdomen. One follow-up MRI showed some tumor shrink after chemo course. She came to radiation oncology clinic and continues to complain the worsening headache. After radiation oncologist's assessment, she was considered a good candidate to receive stereotactic radio surgery (SRS) treatment while chemo therapy is in hold. Regarding her three mets in brain, single iso-mutiple mets technique was considered as the first option for her. Mrs. A brain MRI images before and after treatment are demonstrated in **Figures 1(a)-(f)**.

The patient was treated at 15 Gy in 1fx and three non-coplanar arcs were used. This dose was prescribed within the consideration of the previous 30 Gy whole brain irradiation. Volumetric modulated dynamic arc plan was created in Eclipse (From Varian Medical System, Palo Alto, USA). The isocenter was placed at an almost geometric center of whole brain. From the MRI images in **Figure 1(d)**, the distance from Met1, Met2 and Met3 to ISO is about 3.7 cm, 2.93 cm and 6.11 cm respectively. The Met1 is about 0.8 cm in the largest dimension; Met2 is about 1 cm in diameter; the Met3 is about 1.8 cm in the largest dimension. The PTV was generated at 1 mm margin from GTVs uniformly. The TrueBeam Stx (From Varian Medical Systems, Palo Alto, US) and Exactrac (From BrainLab, Munich, Germany) are used during the treatment.

Patient B:

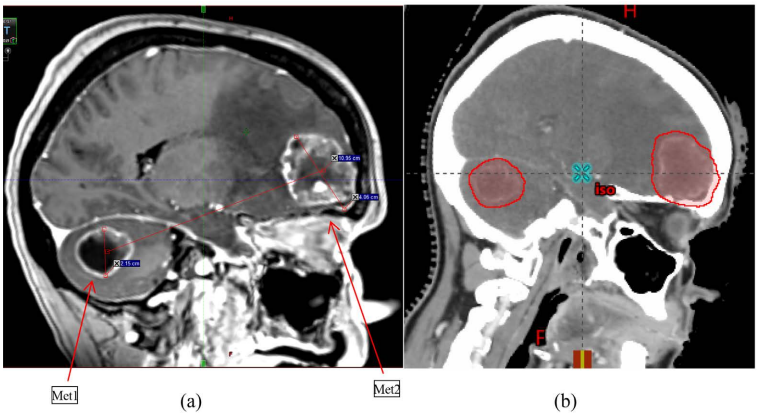


Figure 2. Mrs B MRI image and two Mets geometric dimension (a); Eclipse planning isocenter placement diagram (b).

The 69 years old lady Mrs. B had breast cancer 25 years ago and had both left breast lumpectomy and right breast lumpectomy then. The post lumpectomy radiotherapy was performed at 50.4 Gy in 28 fx. Recently she was diagnosed with Stage IV lung cancer and then systemic palliative chemo therapy was administered. She tolerated the chemotherapy well without major side effect. Her PET/CT showed decrease FDG based right upper lobe lesion. Overall she is doing well until recently she complained about some confusion, severe headache, memory

loss and sometime vomiting. Contrast enhanced CT and MRI were prescribed and revealed that one big lesion on right frontal lobe and other big lesion on cerebellar region. Regarding her tumor size and location, fractionated SRS was recommended. The single-isocenter technique was used to treat two Mets at the same time. The TrueBeam Stx (From Varian Medical Systems, Palo Alto, US) and Exactrac (From BrainLab, Munich, Germany) are used during the treatment. Mrs. B's brain MRI was followed at the time of SRS procedure in Figure 2.

The Met1 and Met2 are about the size of 2.15 cm and 4.06 cm respectively are about 11 cm apart. The isocenter was placed approximately at the middle between two Mets. Therefore, each Met to ISO distance is about 5.5 cm. Each Met distal edge to isocenter is about 8.5 cm. The volume of Met1 is about 7 cc and the Volume of Met2 is about 33 cc. The patient was treated at 30 Gy in 5 fx. The treatment plan was created by 3 non-coplanar volumetric dynamic arcs in Eclipse. The PTV was generated at 1 mm GTV expansion margin uniformly.

Patient C:

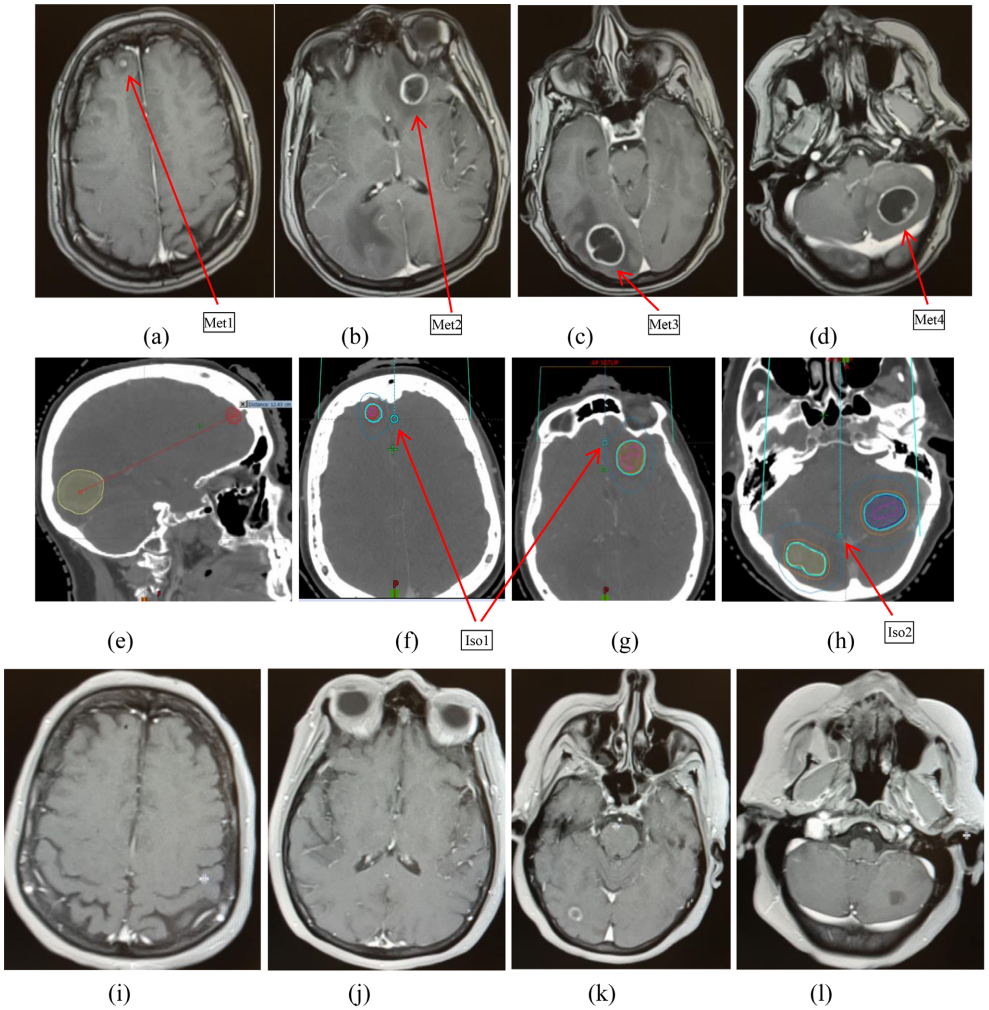


Figure 3. Ms. C MRI pretreatment images Met1 (a), Met2 (b), Met3 (c), Met4 (d); CT images for four Mets geometry dimension (e) and two isocenter placement (f), (g), (h); Ms C MRI post treatment images for Met1 (i), Met2 (j), Met3 (k), Met4 (l).

Ms. C is 78 year old lady who lived in local area with long smoking history for 55 years. She complained of chest pain to her family doctor in January 2019 and then a PET/CT was prescribed for her whole lung scan. It showed three large long masses with mediastinal and lower neck adenopathy. It is also seen large area of edema on the CT scan. After biopsy she was diagnosed with stage IV lung adenocarcinoma. The following brain MRI was immediately performed right after lung diagnosis. Four brain metastases were clearly presented in the MRI images with three large ones and one small one. The largest one is 3.2 cm in the right occipital lobe with surrounding vasogenic edema. The smallest one is 0.7 cm in frontal lobe. Other two are about 2.5 cm each in diameter. Recently Ms. C reported frequent headaches, nausea, dizzy and vomiting. She came to radiation oncologist clinic for pursuing a radiotherapy treatment. Her brain Mets MRI images pre and post-treatment and planning isocenter placement are shown in **Figure 3**.

Four Mets are spread out in the front lobe and occipital lobe and their maximum separation is about 12.4 cm. if we use SIMT technique and place single-isocenter in the geometrical center, the distance between the Met to isocenter can goes to about 6.2 cm in maximum. Due to the large separation among four Mets, we decide to separate them into two groups. Met1 and Met2 are in one group and Met3 and Met4 are in other groups. They were treated in two separate plans. Each plan was prescribed to 30 Gy in 5 fx. It was planned in Eclipse. The GTV expansion margin to PTV is 1mm in all directions. The TrueBeam Stx and Exactrac are used in the treatment.

3. Results

Patient A: Three Mets are displayed in **Figures 1(a)-(c)** and they are shown as three white spots in SRS pre-treatment MRI at T1 with contrast image. **Figure 1(d)** demonstrated the isocenter placement location at one slice of CT image. Because the three Mets are not in same plane, this diagram only gives the estimated distance. In the early phase of SIMT treatment in the small freestanding clinic practice, we followed some big hospitals' practice guideline. We choose the brain geometric center as the isocenter regardless of the distance between target and isocenter. This strategy tried to avoid isocenter shift during the multiple plan treatment when image alignment was used. It also can save some patient-specific QA time. Even if the Met3 is above 6.0 cm away from the isocenter, we still choose to use single-isocenter. The CTV expansion margin to PTV is 1 mm.

Figure 1(e) and **Figure 1(f)** are the post-treatment one year follow up MRI images. From **Figure 1(e)** the Met1 and Met2 (even scroll to different slices) are not visible anymore. It is most likely associated with the adequate radiation treatment which includes the right prescription dose after whole brain irradiation, proper fractionation, proper dosimetry coverage, proper margin and accurate image aliment. From **Figure 1(f)** the Met3 is clearly visible in the follow-up MRI. The Met3 local control failure might have some complicated radiobiological and tumor response interpretation from medical aspect. From physics and dosometry aspect, the distance to isocenter and the 1 mm margin are highly sus-

picious factors and cause the inadequate dosimetry coverage when the table, gantry and collimator rotate during the treatment. Therefore it increased the risk of local control failure of this Met3. Because we tested our LINAC that the 1mm rotational uncertainty only can be held when the distance to isocenter is less than 6 cm for SIMT treatment. This test has been developed and published several months after this patient's treatment [9].

Patient B: **Figure 2(a)** demonstrated the geometry size of Met1 and Met2 and isocenter placement in the Eclipse. The Met1 is about 2.15 cm and Met2 is about 4.06 cm in one dimension. The separation between the two Mets is about 11 cm when we measure distance between two geometrical centers. At the early learning phase of the SIMT implementation in one free-standing clinic, we placed the isocenter at the geometry center between the two Mets. The GTV expansion margin to PTV is also 1 mm. She finished the fractionated stereotactic radiotherapy in the free-standing clinic. First a couple of weeks after the treatment, she felt very well. Later on, she felt some confusion and hard to balance herself. A new MRI was ordered and found that the Met1 remains the almost same size but Met2 size was increased and midline was also shifted. The patient was taken to big university hospital and craniotomy and resection were performed in the Met2. It is obviously that the Met2 was not successfully controlled by our fractional SIMT treatment. In addition to the complicated radiobiology and other medical interpretation of this failure local control, one very natural doubt occurred to medical physicist is that the distant to isocenter might be too big. The 1mm margin might not adequate to account for uncertainty during treatment therefore it caused dosimetry under coverage. The distance between Met1 and Met2 target center to isocenter is about 5.5 cm but the distance between the distal edge of target to isocenter is about 8.5 cm. it is about the distance of Winston-Lutz-Gao test result limit in our LINAC.

Patient C: **Figure 3(e)** demonstrated the separation between two Mets group with maximum distance is about 12.43 cm. **Figure 3(f)** and **Figure 3(g)** demonstrated the isocenter location in frontal group. **Figure 3(h)** demonstrated the isocenter location in the posterior group. Since the two isocenters are used, the maxium distance of each Met to isocenter is less than 4 cm. **Figures 3(i)-(l)** showed 6-month follow-up MRI images. It is clear to see that Met1 shrank into a tiny spot with size less than 5 mm in image (i) and it has almost no affection on brain normal functioning. The Met2 is completely disappeared from image (j). Met3 shrank into a small volume about 20% of its original size. Met4 also reduced volume tremendously. All the four Mets have very positive response to the fractional SRS treatment. There was no indication of radionecrosis and patient felt pretty well and has no neurologic symptoms. From medical aspect the appropriate prescription dose and fractional treatment schema are important in the successful local control of the four Mets. From physics and dosimetry aspect, the two isocenter strategy and proper grouping of four Mets into two groups assured the 1mm is always valid during the non-coplanar arc treatment. It is clearly associated with the success of local control.

4. Discussion

It is well known that the local control failure or success of any cancerous tumor is attributed to the tumor response and dosimetry coverage. This has been proved by about a hundred years' practice of radiation medicine. Tumor response is determined by radiobiology and patient-specific health situation. It is beyond the scope of this study. This study focuses only on the accuracy of dosimetry coverage. The dosimetry coverage is directly affected by the gross tumor volume (GTV) expansion margin which is used to generate planning tumor volume (PTV). The GTV expansion margin is used to account for CT simulation uncertainty, image registration uncertainty, contrast used or not in CT and MRI image, planning system volumetric uncertainty, the LINAC axis rotational error, image guidance error, patient setup uncertainty, target moving uncertainty, etc. Among them, the LINAC rotational error and image guidance error are the most unpredictable ones to affect GTV margin expansion, especially when the tumor is off-isocenter in the SIMT treatment. The LINAC rotational errors depend on LINAC type, age, quality assurance frequency and accuracy, table quality, and patient weight. The older LINAC will have larger uncertainty than the newer generation LINAC. Worldwide, Varian 21EX, 21iX, Trilogy, Novelis Tx, TrueBeam Stx, Edge and Elekta Synergy, Versa HD, Infinity, and Harmony are all have been used to deliver SIMT treatment. Some LINACs are used to deliver SIMT without CBCT, or Exactrac, or surface imaging guidance. Per author's personal experience, all Varian 21Ex, 21iX, Novlalis Tx and TrueBeam Stx have been used to deliver SIMT treatment in brain. Our Varian 21Ex off-Iso Winston-Lutz test has been published several years ago [10]. The institute which implements SIMT technique varied from free standing clinic, community hospital, to University hospital, VA hospital, and government hospital. In a good implementation of SIMT, the medical physicist should perform the physical measurement and analysis to generate the "offset vs. target off-iso distance curve" in their own LIANC. Each institute should create the margin expansion guideline per their own simulation, planning, treatment, IGRT equipment. This guideline should be LINAC-specific and institute-specific. It is strongly not recommended to use the expansion margin from other LINAC and other institutes. The expansion margin from GTV to PTV is based on what your LINAC and institute can achieve, not what planner or physician wants. From literature it is ranged from 0 mm, 1 mm, 2 mm, 3 mm uniform or non-uniform expansion from different LINAC in different institutes.

Due to the limited quantitative knowledge of model based radiobiology and limited clinical trials of hums kind, radiation oncology is still far from accurately predicting the outcome of radiation therapy for each individual patient. Here the author first time proposed the principle "AHARA" in radiation oncology field which is analogy in the radiation protection field "ALARA". It means "As High As Reasonably Achievable" in each step of the radiation oncology practice. It should start with accurate and repeatable patient position during simulation,

proper technique for high-quality image acquisition, very fine target delineation, optimum treatment plan design, robust quality assurance on radiation delivery device, and precise and smooth radiation delivery process. Nobody knows which step is more critical than the other one in the dosimetry coverage but the integration of all steps will definitely impact the dosimetry coverage therefore the local control.

As to the SIMT treatment, many researches [9]-[16] have investigated the relationship between target distance to isocenter, expansion margin and dosimetry coverage in either retrieves model study or physical measurement. Overall their conclusion is that the distance to isocenter will directly affect the dosimetry coverage and 1 mm margin which was originally recommended by AAPM for treating single-isocenter single target is not adequate for SIMT for large distance to isocenter. From the failure and success of local control of three cases in this study, the above conclusion is strongly supported. The similarity of the three cases is that all Mets in brain are not prototype cancer and they are secondary malignancy from other cancer sites. The differences among them are tumor size and geographic locations in addition to medical aspect.

Patient A: Three same kinds of Mets are located in the same brain and same patient and they were irradiated at the same time. They all experienced whole brain radiation. Two of them are controlled very well and one of them failed. A very natural question arise "is this because the third Mets too far from Iso?" From Winston-Lutz-Gao test, it is clearly indicated the 6 cm is the limit to hold the 1 mm margin during the treatment. This treatment does not adhere with "AHARA" principle. It was easy and reasonable achievable to re-group these three Mets into two groups. It would be optimum practice to use one isocenter to treat Met1 and Met2 and other isocenter to treat Met3.

Patient B: The distance between two Mets and volumes of each Met should be taken into account when we design the treatment plan if the AHARA principle was adhered to. Because of large separation between two Mets (center separation about 5.5 cm, distal edge separation about 8.5 cm) and big volume of each Met (Met1 about 7 cc, Met2 about 33 cc), each Met should be treated at individual isocenter or each Met should be treated at different margin. Then the dosimetry coverage would be guaranteed. The dissection of Met2 was directly caused by the local control failure of fractional SIMT technique in this circumstance.

Patient C: Because the four Mets are separated into two groups and treated in Iso1 and Iso2 respectively, the maximum distance between each Met and its own isocenter is less than 4 cm and we believe that the 1 mm GTV expansion margin was held pretty well during the non-coplanar arc treatment. Therefore the 1 mm GTV expansion to PTV is adequate and assured proper dosimetry coverage for all four Mets. This has been proved by our previous study [10]. The two groups and two isocenter treatment strategies met the AHARA principle for this patient treatment in which the total treatment time is about 40 minutes. The treatment time which includes isocenter shift, CBCT re-verify, Exactrac alignment and

beam delivery is longer than SIMT but is still reasonably achievable for this patient. This case clearly indicated that the SIMT technique has a limitation that the distance between target and Isocetner must be taken into account because it directly impacted the rotational uncertainty and how much margin you should use when you design the plan. The reasonable distance between each Met and isocenter assured the appropriate margin we used. It is associated with the success of local control of brain metastasis for this patient.

5. Conclusion

Our early learning experience in three real patient cases strongly supports the conclusion that the distance to isocenter directly affects the margin, inappropriate margin increase the risk of local control failure in LINAC-based single-isocenter SRS or SRT for multiple brain metastases. Even though three exception cases are presented in this study, more similar cases study will be performed in the future. The GTV expansion margin should be LINAC specific and institute specific and we strongly do not recommend adopting margin from other LINAC and other institutes. The AHARA (as high as reasonably achievable) principle should have been adhered to in the single-isocenter multiple target (SIMT) radiation therapy process in every patient.

Conflicts of Interest

The author declares no conflicts of interest.

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