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# INITIAL HFRT EXPERIENCE ON TREATING LARGE BRAIN METASTASES LESION: A CASE REPORT

**Hadi Nurhadi**[1]

1. Radiation Oncologist Of Regional General Hospital of West Nusa Tenggara Province

## Abstract

Brain metastases in cancer patients are increasing, due to advances in imaging and systemic treatment. Stereotactic Radiosurgery (SRS) is a high-end radiotherapy technique that is preferred to treat small brain metastases. Hypofractionated Radiotherapy (HFRT) is an alternative technique that demand lower requirements and ideal for treating larger brain metastases. This case report intended to report our institution initial experience using HFRT in limited setting to treat a patient with large brain metastases. Here we report a case of 43 years old women with previous breast cancer history was admitted with general weakness and severe headache since 2 weeks before admission. A CT scan exam shows multiple metastatic lesions on both parietal lobe, the largest lesion measures ≥ 3cm in diameter with a prominent vasogenic edema that caused lateral ventricle compression and mild midline shift. SRS is preferred to treat brain metastases due to its efficacy and excellent therapeutic ratio. Unfortunately it has limitation in treating large metastatic lesions. For such lesions, HFRT being a simpler radiation technique can be opted to achieve acceptable local control and low toxicities profile. We use HFRT to treat a patient with large brain metastases lesion using IMRT with 10 x 4Gy fractionation scheme. The evaluation results 6 weeks later shows no viable brain lesion without any cognitive deterioration reported. HFRT for large brain metastases treatment is safe and viable to conduct in institution with limited resources. This relatively simpler technique compared to SRS should be considered to achieve acceptable therapeutic ratio with minimal toxicities.

Keyword : Brain metastases, SRS, HFRT, Breast cancer

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## Introduction

Brain metastases is increasingly common to be found in late stage cancer, such as predicted to be a result from ongoing improvement in systemic disease treatment and the ability of neuroimaging modalities[1]. For more than 60 years Whole Brain Radiotherapy (WBRT) has been commonly used to treat patients with multiple brain metastases, mostly due to its efficacy in palliation and ease of delivery[2]. However, recent developments and clinical trials unveiled WBRT is less effective for treating larger metastatic lesions[4]. In the other hand WBRT is associated with post radiation toxicities namely cognitive decline[3]. Consequently, Stereotactic Radiosurgery (SRS) is much favored to treat brain metastases for its effectiveness in providing adequate local control and limited neurocognitive toxicities. However, SRS is not always doable, in one hand delivering a very high dose of radiation in one single dose is difficult in large metastatic lesions (≥3cm or ≥4cm in diameter), usually limited by the acute and late side effect on adjacent normal organs[6]. On the other hand, Stereotactic Radiosurgery need a very sophisticated treatment units, preferably a state-of-the-art Linear Accelerator with a high number of thin MLC leaf (2,5 mm – 3 mm in thickness) to provide a highly modulated irradiation technique with excellent isodose curve and quicker treatment time.

Hypofractionated radiotherapy could be chosen as a primary treatment for large brain metastatic lesion, in which several high dose of radiation is administered in several fractions. Thus by lowering the radiation dose and being divided in several fraction, the dose restriction on organ at risk is much more flexible. Meaning a lower irradiation technique delivered by a less sophisticated treatment unit to achieve an acceptable therapeutic ratio is feasible. This case report aims to report our institution first experience using hypofractionated radiotherapy in limited settings to treat a patient with large brain metastases lesions and the result afterward.

## Case Report

A-43 years old women with previous breast cancer history was admitted to West Nusa Tenggara General Hospital with general weakness, unknown seizure history, and severe headache since approximately 2 weeks before admission. A CT scan exam (*figure 1.*) with contrast shows multiple metastatic lesions on both parietal lobe, the largest lesion measures around 4,3cm x 3,6cm x 3,1cm with a prominent vasogenic

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edema along the left frontal lobe that caused lateral ventricle compression and mild midline shift. High dose dexamethasone is administered, and the patient was admitted to receive radiotherapy.

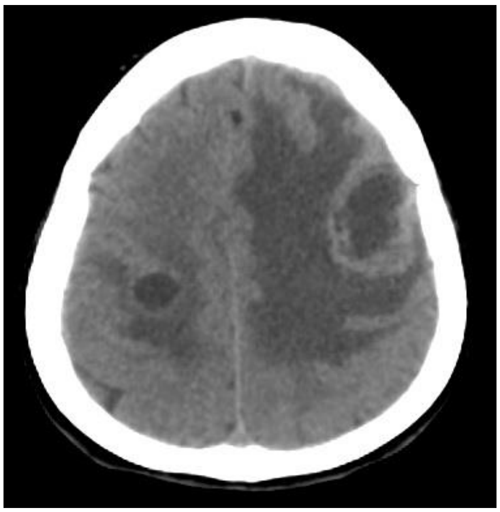

Figure 1. CT scan Exam with contrast display multiple metastases lesions, with > 3 cm in largest diameter.

The patient was immediately treated using hypofractionated radiotherapy (HFRT), using IMRT beams to deliver 40 Gy of radiation dose in 10 fraction of irradiation. Six weeks after the last fraction, another CT scan exam was taken to evaluate the results of radiotherapy, there was no apparent enhancing lesion on the right nor the left parietal lobe, vasogenic edema is greatly reduced, ameliorating the midline shift and lateral ventricle compression.

**Discussion**

Brain metastases has become more frequent in oncologic patients, with an estimate 20% of these patients shall develop brain metastases[7]. Patients with brain metastases could have a single (solitary) metastasis or numerous lesions present on CT or MRI imaging, they might be diagnosed with brain metastases in the absence of any symptoms[8]. On the other hand, those with symptomatic brain metastases could have a manifestation akin to those of other mass lesion in the brain such as headache, nausea, seizure and neurologic disorder[8].

Surgery is considered to be the cornerstone on treating brain metastasis, unfortunately despite the progress in surgical techniques, surgery alone for brain metastases lesions results in unsatisfactory local control rates[9]. Another option in treatment such as WBRT, has been considered to be the standard of care for patients with solitary or multiple brain metastasis who is unable to undergo surgical resection[1]. However, recent developments and clinical trials unveiled WBRT is less effective for treating larger metastatic lesions[4]. Nieder et al.[10] analyzed the effectiveness of WBRT in controlling 336 brain metastasis in 108 patients, it was found that local failure was approximately 48% in

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tumors measuring < 0,5 $cm^3$, however all lesions measuring > 10 $cm^3$ recurred. WBRT is also correlated with post radiation toxicities such as cognitive deterioration. WBRT could induced significant decrease of cerebral microvascular density in hippocampus, a region in the brain that is dominant for learning and memory[5]. These cognitive deterioration including memory recall impairment and worsening verbal communication could occur between 1 to 6 months (or much later) after brain metastases treatment[5].

Breakthrough in radiotherapy treatment units and devices gave birth to Stereotactic Radiosurgery (SRS), a technique which could deliver a very high dose of radiation in a very conformal manner. As such, SRS could provide as an exceptional minimally invasive ablative therapy to treat brain metastases lesions. Patient who received SRS could avoid the risk of surgery-related morbidity, and typically chosen over surgery for cases with small, asymptomatic lesions or for patients with inoperable lesions[8].

The efficacy of SRS alone in treating limited brain metastases lesions has been acknowledged by many phase III randomized trials comparing SRS alone to SRS plus WBRT. Generally, most of these studies display similar overall survival, quality of life and superior cognitive preservation with SRS alone compared to SRS plus WBRT[8,11-12]. However, SRS is not always doable, to deliver a very high dose of radiation in one fraction could be arduous in treating large brain metastatic lesions (≥3cm or ≥4cm in diameter) due to the limitation of acute and late side effect on adjacent normal organs[6].

High accuracy and conformity are crucial in SRS, as to fulfill such demand a dedicated Linear Accelerator is needed. To deliver an ideal SRS technique, a Linear Accelerator should be equipped with a high number of thin MLC leaf (micro-collimator or high-definition multileaf collimator) which measures 2.5 mm – 3 mm in thickness to provide a minimum dose leakage and small consistent penumbra, hence a very high conformity index which is befitting for high dose resolution SRS[13]. To provide high accuracy during SRS treatment, a sophisticated patient monitoring technology such as Electronic Portal Imaging Device (EPID) and/or Cone Beam CT is also needed. These aforementioned features is typically found in an advanced Linear Accelerator, which could be difficult to have in a limited setting.

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Due to the difficulties in managing large metastases lesion, numerous research has been conducted on the delivery of large doses of radiation in a few fractions. Commonly as a trial to increase the biologically equivalent dose (BED) delivered to brain metastases lesions and to increase local control while minimalizing the risk of radiation induced toxicity. While this alternative to SRS demands the patient to go through many days of treatment, some research have exhibit that fractionated stereotactic radiation therapy provides high local control rates, around 66% to 91% at one year of evaluation[15]. In HFRT radiation dose is reduced by dividing them into several fraction, this could provide leniency on dose restriction and treatment planning. Meaning that a lower tier Linear Accelerator could be used to achieve sophisticated theraupeutic ratio.

HFRT was found to be a safe and beneficial treatment option for patients with large brain metastases. Jiang et al.[15] published the outcomes of 40 patients with brain metastases larger than 3 cm (3.1 cm – 5.5 cm) treated with HFRT, with 40 Gy as median prescribe dose and a median of 10 fractions to the 90% isodose line. The overall survival rate in one year was 55.3% without any acute toxicities found and a high Karnofsky Performance Score of 80 and above[15].

A number of clinical trials perceive that the local control on large brain metastasis conferred by HFRT could be higher or at least comparable to SRS[15,16]. A trial by Feuvret et al.[15] demonstrate the results of 36 patients treated for single brain metastases lesion larger than 3 cm in diameter (median diameter 3.7 cm), with either HFRT or SRS. These patients were divided into two groups which receives either 14 Gy in one fraction or 3 fractions of 7.7 Gy[15], resulting in 100% of one year local control rates in patients treated with HFRT vs. 58% of one year local control rates in patients treated with SRS[15].

Another research by Fokas et.al.[16] comparing the effectiveness dan radiation toxicity on 260 patients with 1–3 brain metastases lesions who were treated using either SRS (median dose 20 Gy; n = 138) or two different HFRT dose concepts: 7x5 Gy (n = 61) or 10x4 Gy (n = 61). The 1-year local progression-free survival (LPFS) was found to be 73, 75 and 71 % for the aforementioned treatment groups[15]. On this case SRS was found to be correlated with higher radiation toxicities (grade I-III) compared to HFRT[15]. These results may indicate that HFRT could provide better local control rate because it

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allows the application of high radiation dose to large lesions or particular metastases lesion located near critical structure that is either unsuitable for SRS or needed to lower the SRS dose which could jeopardize local control[15].

Our patient had multiple metastases lesion, with a largest lesion of 4,3cm x 3,6cm x 3,1cm at the left frontal lobe. Accordingly we choose HFRT to treat such lesion, mainly for it's capability to treat larger lesion without notable radiation toxicities and due to our treatment unit limitation. The prescription dose is 4 Gy delivered in 10 fractions. This fractionation scheme was chosen since it has the safest toxicity profile[16]. The patient was immobilized for simulation and treatment using a non-invasive double thermoplastic head mask. Computed tomography (CT) images were reconstructed at 2.5 mm slice thickness on a Phillips Brilliance Big Bore CT Simulator.

An IMRT (Intensity Modulated Radiotherapy) plan was generated in Eclipse External Beam Planning system ver. 13.7, using seven X-ray energy beams of 6 MV with a dose rate of 400 MU/minutes (*Figure 2.*). A higher number of beams resulted in better isodose outcome, but longer treatment times. We chose a lower usage of beams with the shortest treatment to ensure minimal target movement. Using IMRT we could only achieve a 120% PTV Dmax, a higher benchmark for maximum dose resulted in worse isodose distribution. This plan was delivered on a Clinac CX (Varian Medical Systems) equipped with 2.5 mm MLC leaf in the center and 5 mm outer MLC leaf.

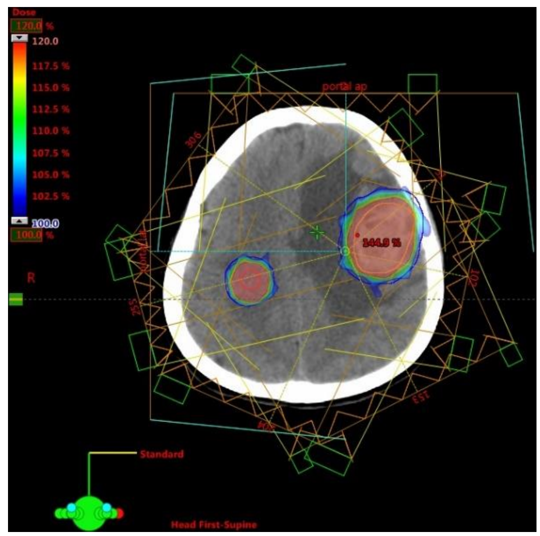


Figure 2. An IMRT plan was generated, using 7 x-ray beams beams of 6 MV and 400MU/min dose rate.

The patient returns 6 weeks later for an evaluation, a head CT scan exam with contrast was done (*Figure 3*). There was no apparent enhancing lesion of both parietal lobe, vasogenic edema and midline shift was greatly reduced, leaving only a hypodense lesion on the left frontal lobe (possibly hematoma or post radiation necrotic tissue). Clinically the patient does not display any cognitive deterioration symptoms and has a high Karnofsky Performance Rate.

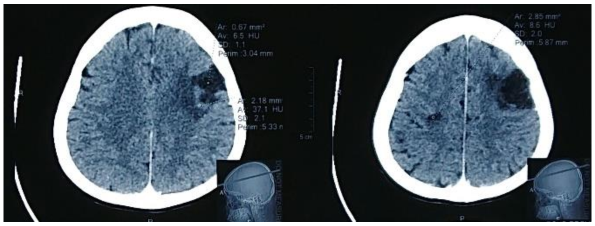

Figure 3. An evaluation CT with contrast was taken, no apparent enhancing lesion was found, vasogenic edema and midline shift was reduced.

## Conclusion

HFRT is safe and beneficial treatment alternatives for patients with large brain metastatic lesions. Due to its less demanding requirements, HFRT could be done is a much more limited setting. As in our case using a relatively simpler IMRT technique could resulted in an acceptable local control with a low radiation toxicity, on par with the results delivered by SRS. In which could retain a high quality of life for patients. In that capacity HFRT should be considered in treating patient with large brain metastases, even in an institution with limited settings.

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