CASE REPORT

Sterotactic surgery for multiple brain lesions: a paradigm shift

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SUMMARY

Brain metastasis are common and may be multiple. This often results in a dilemma in treatment. Prior to this, the understanding of the role of stereotactic radiosurgery such as Gamma Knife is limited to three or less brain metastasis. A paradigm shift has occurred in Malaysia whereby stereotactic radiosurgery is now being used for the treatment of multiple brain tumours exceeding ten lesions. A seventy-year-old gentleman with small cell lung carcinoma and more than thirty brain metastases underwent Gamma Knife treatment for his brain lesions post chemotherapy. There was resolution of cerebral lesions with small residual at the left cerebellum. He had no adverse side effects. Therefore, stereotactic radiosurgery is now being used for multiple brain metastatic lesions as it provides improved palliation, less neurocognitive deterioration with improved quality of life. This discovery places whole brain radiotherapy for the treatment of metastatic brain lesions as a treatment of the past.

INTRODUCTION

Brain metastasis is common for lung, breast and gastrointestinal tumors. Up to 40% of patients with cancer will experience brain metastasis.[1] This becomes a dilemma as metastatic lesions are often multiple, surgically inaccessible, decrease length of survival and ultimately results in poorer prognosis. The cerebrum is most commonly affected (85%) followed by cerebellum (10-15%) and brainstem (up to 3 %). Gamma Knife (GK) was first used to treat a recurrent solitary brain metastasis of a cerebral hypernephroma in 1989.[1]

The initial understanding of the role of stereotactic radiotherapy such as Gamma Knife (GK) is to provide a concentrated and targeted stereotactic beam to a small single lesion within the brain which is inaccessible by surgery, or if surgery will cause more morbidity to the patient. However, this poses a dilemma for patients with multiple brain lesions or metastasis whereby the primary site has been dealt with. Prior to this many have thrown in the towel after chemotherapy or when other modalities of systemic therapy have failed, leaving the patient on the palliative pathway. GK stereotactic radiosurgery has been prescribed in 3-4 small brain metastasis. What about multiple brain metastasis exceeding four lesions? Therefore, the aims of this manuscript are to discuss the feasibility of GK radiosurgery for multiple brain metastasis of 10 or more lesions; its advantages and disadvantages and to debunk the current myth of GK in treating a sole metastatic brain disease.

CASE PRESENTATION

A seventy-year-old chronic smoker was diagnosed with metastatic small cell lung carcinoma. At presentation, he had extensive disease involving the lung, mediastinal lymphadenopathy, liver and brain metastases. Prior to his illness, he had no medical illness. He spent majority of his life in United Kingdom where he studied and worked as an analyst. He lived alone and led an independent but active life. He developed imbalance three months prior with worsening gait one week prior to his presentation. Besides, he had expressive dysphasia which was progressive over a three month period.

Magnetic Resonance Imaging (MRI) showed multiple brain metastasis of more than 30 lesions (Figure 1) with a total brain volume of 9.261cm^3. He was given options of whole brain RT or GK, but opted for GK stereotactic radiosurgery (Elekta AB, Stockholm) treatment in October 2020. The lesions were treated with a range of 22-30Gy at 50% isodose, single fraction over three days. The brain metastasis protocol via a double contrast MRI was adopted. He was observed overnight in hospital.

Two weeks after GK, he commenced on etoposide/platinum chemotherapy. He had remarkable response clinically and radiologically each cycle. On clinical re-assessment at two weeks post GK, his imbalance and expressive dysphasia had resolved whereby he resumed a normal gait and could express himself well. CT reassessment after 4 cycles of chemotherapy on December 2020 revealed reduction in the thoracic lesions, mediastinal and supraclavicular adenopathy. Unfortunately, there were new liver metastases. He declined second line chemotherapy treatment.

He developed twitching of the facial muscles some three months later in January 2021. There was however no other new neurological deficit. The MRI of the brain at twelve

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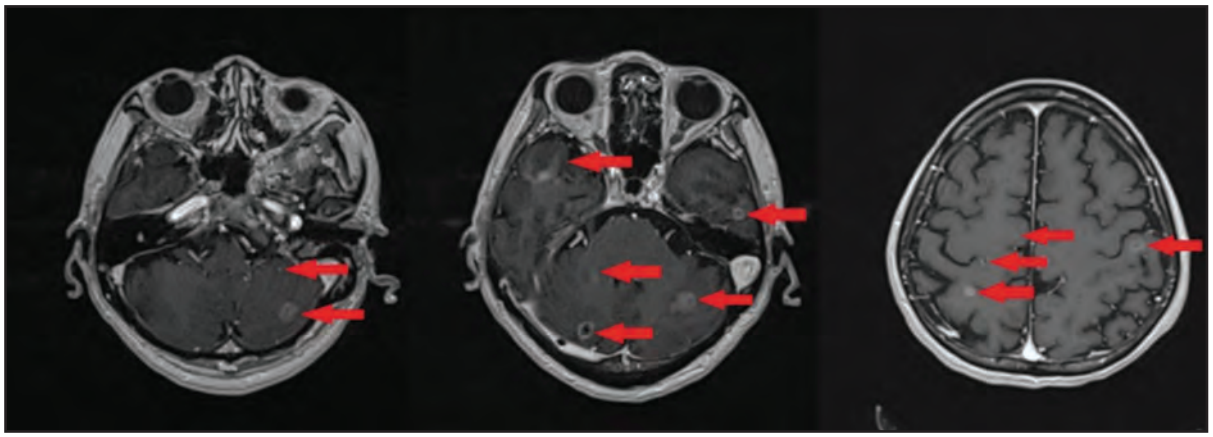

Fig. 1: Axial cuts of MRI showing multiple brain metastasis (red arrows)

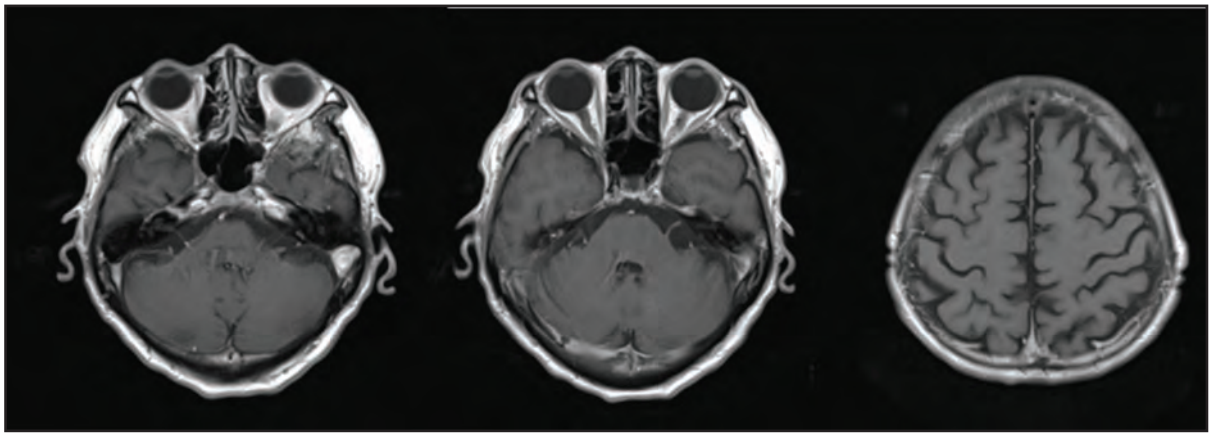

Fig. 2: Previous lesions in Figure 1 were no longer visible post tretment with GK.

weeks post treatment in January 2021 showed resolution of supratentorial grey white matter lesions with minimal residual lesions in the left cerebellum (Figure 2).

He deteriorated from his liver secondary and passed away in April 2021. Despite the disease progression, he managed to maintain his independence and cognition which were his priorities upon deciding treatment

DISCUSSION

This case presents a patient with metastatic small cell lung cancer with multiple lesions to the brain. Although the treatment of multiple brain lesions treated with GK was experimented since the early millennium, this was the first use of GK for the treatment of multiple brain lesions at the Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia since the recent launch of its GK center. As technology improves, many have experimented with pushing the boundaries, resulting in a paradigm shift with greater role for stereotactic radiosurgery. Known assumptions of GK are single fraction radiation for multiple tumors is inadequate for optimal treatment; brain metastasis is radio resistant; stereotactic radiosurgery is limited to cases with 3 or less brain metastases and brain metastases are to be treated with whole brain radiotherapy (WBRT).

Prior to GK, the treatment of the case above will be WBRT with systemic steroids. Median survival rates with WBRT are 1 -2 months. Some have advocated the use of radio sensitizers to increase the sensitivity and uptake of radiotherapy to the brain. However, results were not promising with little or no benefit to tumor size and survival.[2] Andrews et al. 2004 looked into WBRT with and without stereotactic radiosurgery for patients with three or less brain metastatic lesions. Patients with WBRT and stereotactic radiosurgery showed an improvement of medial survival of 5.5 compared to 4.9 months for the WBRT group alone.[3] GK can be used as a salvage treatment for failure of WBRT.

Chang et al. 2009 performed a randomized control trial comparing only stereotactic radiosurgery and stereotactic radiosurgery with WBRT. The stereotactic radiosurgery group with WBRT had brain lesion recurrence within 1 year (73% vs 27%) post treatment but showed higher risk of significant learning and memory decline by 4 months of treatment.[4] In another study of 1194 patients with 5-10 multiple brain metastasis, stereotactic radiosurgery had shown to be not inferior to stereotactic radiosurgery and WBRT with brain metastasis.[5] A Cochrane review by Tsao et al. 2012 recommended the consideration of stereotactic radiosurgery exclusively for brain metastasis in selected patients. Therefore, previously held believe that WBRT radio resistant brain metastases respond to GK with the number metastasis

being limited to less than 10 is now irrelevant with no difference in overall survival.

Questions have been raised about dosage and toxicity of GK stereotactic radiosurgery due to concerns with cumulative radiation when treating multiple brain lesions. Radiation doses are often calculated based on cumulative tumor volumes. Heterogeneous distribution allows for cumulative doses delivered to the whole brain to be small. This decreases its potential toxicity. Whole brain exposure of 8Gy is acceptable and considered non-toxic.[6] Thus, the total GK radiation over multiple sessions and not number of brain metastasis is key in predicting side effects.

Furthermore, there are considerations for repeating GK stereotactic surgery with an interval when multiple lesions are involved as the radiobiological effect of GK is 2.5x than that of fractionated radiotherapy. A total dose of 30-40Gy is delivered by radiotherapy which is equivalent to 12-16Gy in GK stereotactic surgery.[6] Therefore, this shows that dose homogeneity is not essential whereby GK allows gradients aimed to protect surrounding tissue with a low dose distribution for brain metastasis and the ability of dose sculpturing.

Is there a role of stereotactic radiosurgery in post operated brain metastasis? A phase 3 trial by Mahajan et al 2017 compared 68 patients observed post brain resection of up to three brain metastases measuring 4cm or less with 64 patients receiving stereotactic radiosurgery. The observation group had a 43% 12 months' freedom from local recurrence compared to 72% in the stereotactic radiosurgery group.[7] This was the hallmark study that promoted the use of GK in maintaining local control in post resection of brain metastasis.

A review of 3498 patients by Higuchi et al 2018 showed brain radio-necrosis to be less than 3% with GK stereotactic surgery [8]. Stereotactic radiosurgery provides similar survival rates for patients with more than 10 brain metastatic tumors.[8] In the patient above, although there were residual tumors within the left cerebellum, the use of stereotactic GK allowed for good performance status with minimal or no neurological deficit with the exception of an occasional twitching of the left facial muscle, which is an acceptable side effect. This allowed the patient a better remaining quality of life. Most patients will often succumb to the progression of their primary disease, as so did with our patient above. However, the prognostic factors for overall survival and intracranial disease free with single fraction GK is dependent on the initial number of brain metastasis and adjuvant systemic disease administered.[11]

Brain metastasis exceeding 8 to 10mls in size are often best treated surgically.[9] However, patients with brain metastasis who are unable to undergo general anesthesia may be favorable to multiple fractions of GK stereotactic radiosurgery, involving 2 to 3 stages.[10] The adverse side effects of GK are local oedema which are often transient and due to inaccurate planning and high dosage. This has a bimodal distribution whereby it may occur six to eight or twelve months post treatment. Meanwhile factors associated with less side effects are a total volume of the largest brain metastasis being less than 5mls, brain radiation being between 12 to 30Gy; hypo fractionation and no previous WBRT.[9,12] Boundaries have been extended for solitary single metastatic tumour volumes up to 33.5 have shown to respond favorably with less adverse events. Future work explores the role of systemic chemotherapy and immunotherapy with stereotactic radiosurgery for cases involving distant brain control in metastasis to decrease the re-occurrence of new brain lesions.[9]

CONCLUSION

The current use of GK stereotactic radiosurgery can be used for multiple brain metastasis exceeding ten or more lesions with less side effects compared to WBRT. It may offer palliation with better quality of life in patients with advanced primary disease and multiple brain metastases.

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DECLARATION

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