



Dose Escalation with Fractionated Radiosurgery in Oligometastases Brain with Controlled Extracranial Disease: Improved Progression free Survival Outcome

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SUMMARY

Traditionally Whole Brain Radiotherapy (WBRT) has been used in unresectable and oligo/multiple metastases, but the outcomes are not very promising. Here we report eighteen month survival with stable intracranial disease in a case of adenocarcinoma of lung with three metastatic brain lesions after being treated with WBRT with Fractionated Stereotactic Radiosurgery (FSR) boost.

BACKGROUND

Brain metastasis has been reported in 25-40 % of cancers and is associated with fairly dismal outcome with a mean survival period of 6-9 months as reported in various case series. In management of brain metastasis, there is extensive published experience of Stereotactic Radiosurgery (SRS)/ Fractionated Stereotactic Radiosurgery (FSR) with control rates equal to or higher than those for surgery for single/oligo metastasis. The term FSR refers to stereotactically guided delivery of highly conformal radiation to a defined target

volume in multiple fractions (4-5), typically using non-invasive positioning.

CASE PRESENTATION

A 37 year old male, non-smoker was diagnosed with Adenocarcinoma right lung in Jan 2012 stage IB and underwent right lobectomy (pT2cN0M0, EGFR negative, ALK negative) followed by adjuvant chemotherapy (Pemetrexed + Cisplatin) 4 cycles. He tolerated the treatment well with a symptom free period of 1 year. One year later in June 2013 patient developed multiple brain metastasis (right occipital, right cerebellum and left frontal region) size ranging 2.5 -4 cm (figure 1) with no evidence of extracranial disease on PET -CT. Patient was treated with whole brain radiotherapy (WBRT)30 Gy in 10 fractions for the same. Patient presented with worsening of neurological symptoms after one month of completion of WBRT.

INVESTIGATIONS

The patient was advised contrast enhanced MRI brain to evaluate the metastatic brain lesions along

with haematological investigation, Kidney function test, and Liver function test and ultrasound whole abdomen as the baseline investigation. MRI brain was suggestive of brain metastases while rests of the investigations were normal.

TREATMENT

In view of stable extracranial disease and recursive partitioning analysis class I further dose escalation with FSR to all the three metastatic lesions (two supratentorial and one infratentorial) was planned. The patient was immobilised with mouth piece, fraxion frame, vacuum cushion and thermoplastic mask (figure 2) providing high degree of precision. 3 mm CT slices were captured using multi slice CT simulator. Using seven fields dynamic IMRT planning (figure 3) for multiple brain metastases was done using CMS Monaco (Version 3.3) and a total dose of 16 Gy in 4 fractions over 4 days were delivered using 6MV photon on Elekta Infinity. For verification daily Cone Beam CT was done by X-Ray Volume Imaging (XVI) (version 4.5.1) using Volume View (Imaging technique) (figure 4) & Dual Registration such as click box and mask for image registration.

OUTCOME AND FOLLOW-UP

The treatment was well tolerated by the patient, with improvement in his symptoms and reduction in doses of steroids required. Repeat MRI after 3 months (figure 5), 8 months (figure 6), 12 months post radiotherapy revealed stable disease with no radiological progression of intracranial lesions and no neurologic symptoms. Although the primary disease remained controlled bone metastasis in left iliac region were detected on repeat PET-CT (figure 7) scan 6 months post radiotherapy for which patient was given palliative radiotherapy of 800 cGy in single fraction to left hemipelvis f/b 6 cycle of Paclitaxel 280 mg+ carboplatin 750 mg (3 weekly) + Zoledronic acid 4 mg (4 weekly). After 6 cycles chemotherapy patient received tab Erlotinib 150 mg OD for 3 months. Meanwhile MRI brain dated 27.08.14 reported non-progression in three intracranial lesions but there was distance brain failure as a long segment T2 hyperintense lesion in cervical cord extending upto C4 level (figure 8) s/o metastatic spread in cervical cord was seen. With abovementioned treatment patient was relieved of bone pain however succumbed to intercurrent respiratory infection in November 2014, 18 months post radiotherapy.

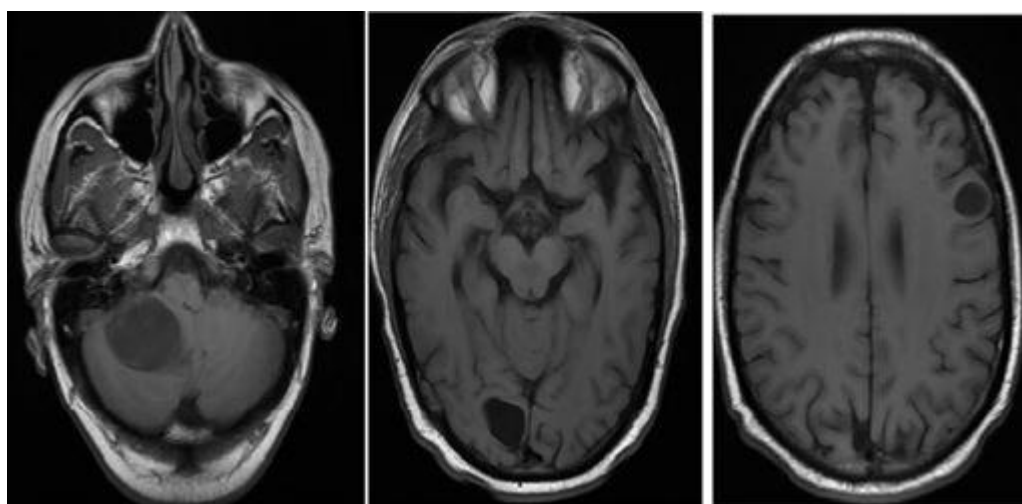


Figure 1- At presentation T1 axial MR images showing hypointense cystic lesions in right cerebellar, right occipital and left frontal region



Figure 2- Noninvasive immobilisation using mouth piece, fraxion frame, vacuum cushion and thermoplastic mask.

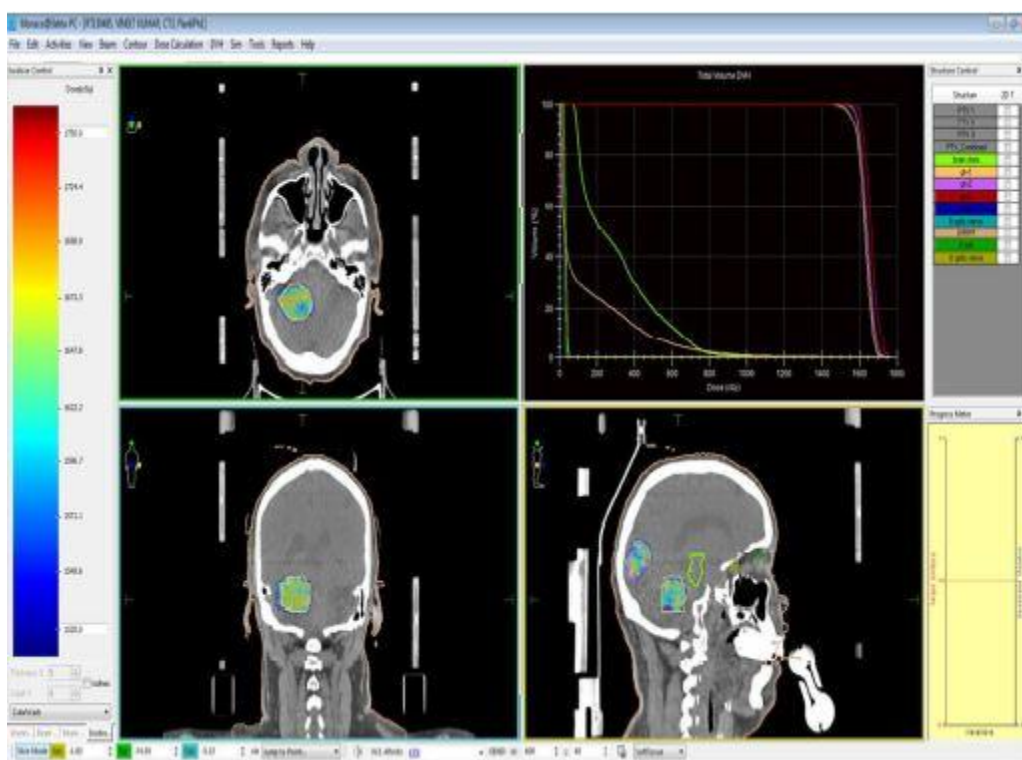


Figure 3- Beams eye view and dose volume histogram for FSR

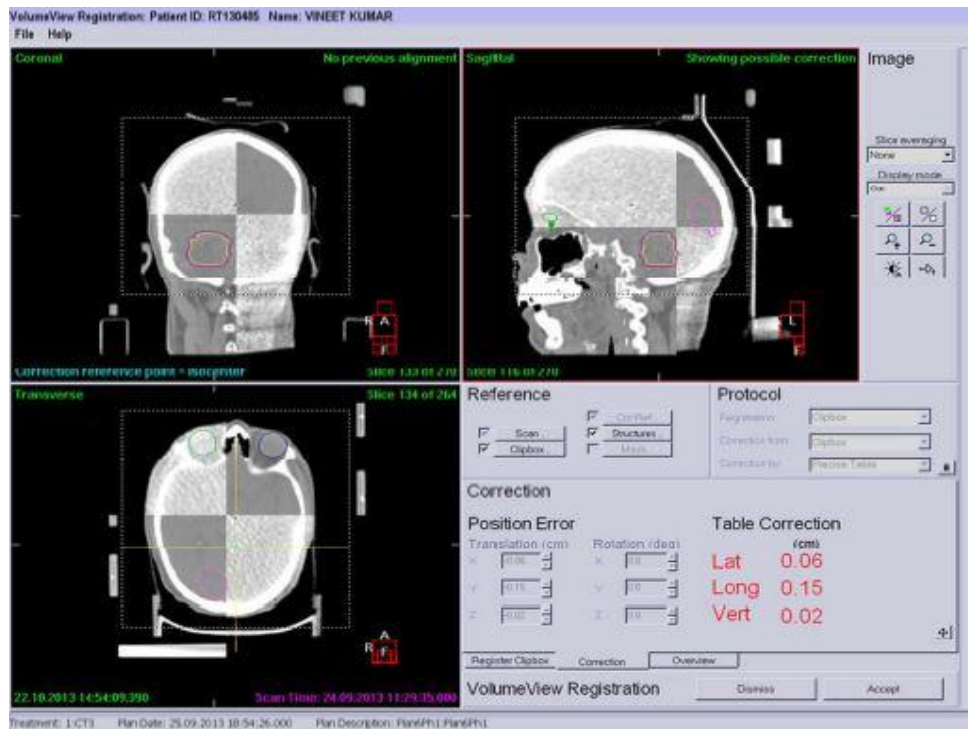


Figure 4- Volume view registration and treatment verification using cone beam CT.

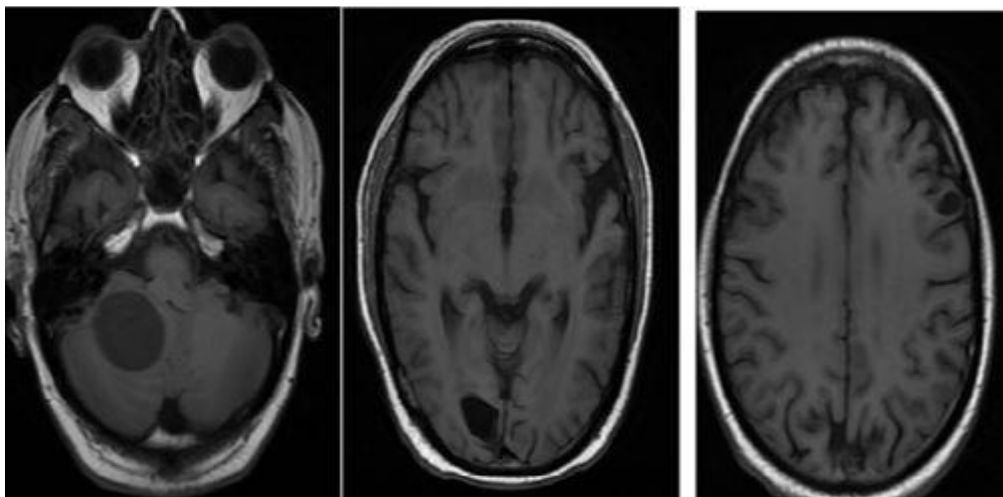


Figure 5- 3 months post FSR T1 MR images showing stable intracranial disease

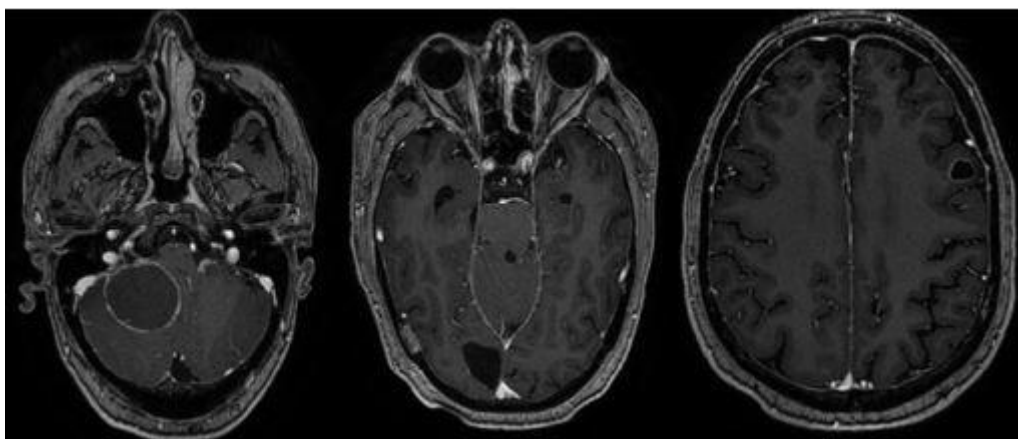


Figure 6- 8 months post FSR T1 MR images showing contrast enhanced margin without any significant perifocal edema or increase in size.



Figure 7- PET CT image showing FDG avid lesion in the left iliac bone with controlled primary disease.

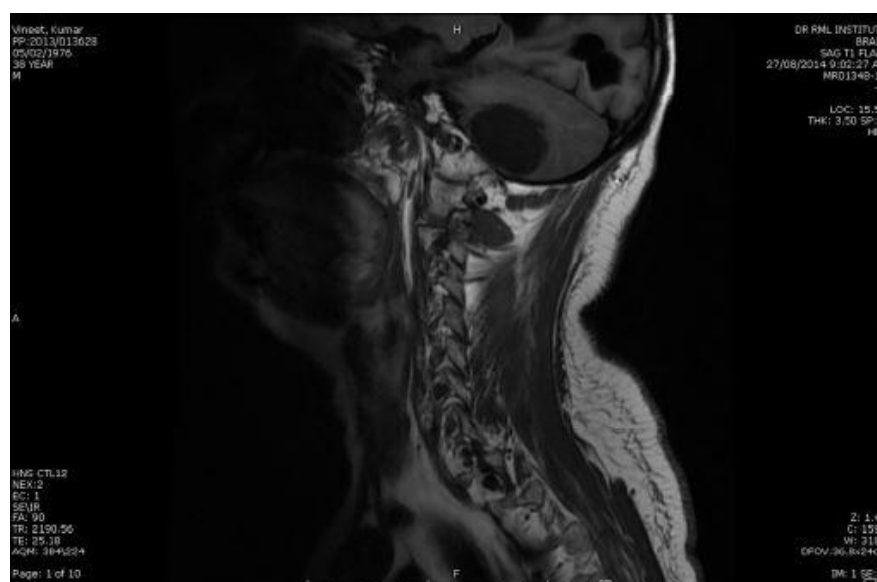


Figure 8- T2 hyperintense long segment lesion in cervical cord extending upto C4 level in MRI spine.

DISCUSSION

The advantage of WBRT + FSR over WBRT alone has been proved in several studies. The RTOG 95-08,^[1] double blinded randomized trial evaluated 333 patients with 1 to 3 metastatic lesions in brain with either WBRT + SRS boost or WBRT alone and found that there was no significant difference in overall survival but improved survival in patients with single lesion treated with WBRT + SRS Boost. On secondary analysis of RTOG 98-05 by Sperduto *et al*,^[2] where only 252 patients evaluable by Graded prognostic Assessment(GPA) were included found survival advantage for patients with GPA 3.5-4

with WBRT +SRS irrespective of 1,2 or 3 metastasis. Pirzkall *et al* (1998),^[3] and Sneed *et al* (1999),^[4] showed improved median freedom from progression with WBRT + SRS as compared to WBRT alone but no improvement in median survival. The large retrospective analysis of 500 patients by Sanghavi *et al*,^[5] showed better median overall survival in WBRT+ SRS boost over WBRT alone. Similar results were observed in a randomized study by Kondziolka *et al*,^[6] and Kocher *et al*,^[7] in EORTC 22952–26001 study showing survival benefit with addition of SRS boost to WBRT. Sahgal *et al*,^[8] in recently published phase III trial comparing WBRT + SRS

against SRS alone showed local control significantly favoured WBRT+ SRS arm ,although for age < 50 year survival favoured the SRS alone arm. The median survival in all these studies varies between 5 to 11 months. As reported by Sahgal *et al* in IPD metaanalysis, risk of distant brain failure is more in patients with >1 brain metastases. Our patient has developed distant brain failure while the three intracranial lesions are being controlled in the treated area. The local brain failure hazard which was lesser with WBRT + FSR was seen in our case sufficing the same observation as the above mentioned study. The symptom free survival of 16 months with multiple brain metastases following WBRT with FSR boost as we report in this case is a rarity and encourages its use in suitable patients.

LEARNING POINTS/TAKE HOME MESSAGES

- WBRT continues to be the standard of care in patients with multiple brain metastases.
- Dose escalation with FSR provides a feasible and well tolerated substitute for conventional surgery in cases of oligometastases of brain with stable extra cranial disease.
- In the light of unexpected prolongation of progression free survival as seen in our case, randomized study adequately powered to establish the efficacy of FSR in brain oligometastases is needed to reinforce the confidence in day to day treatment practice.

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